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The Western Journal of Medicine

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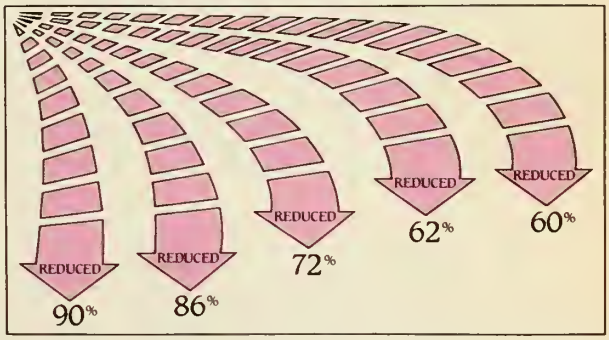

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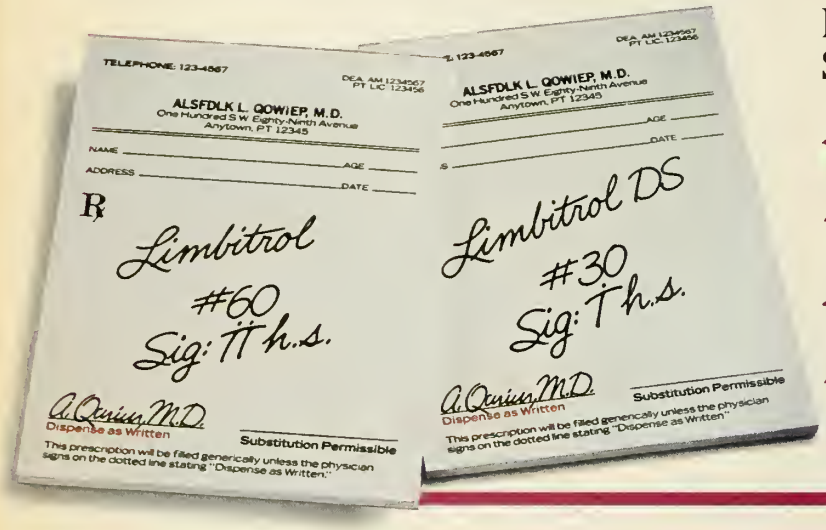

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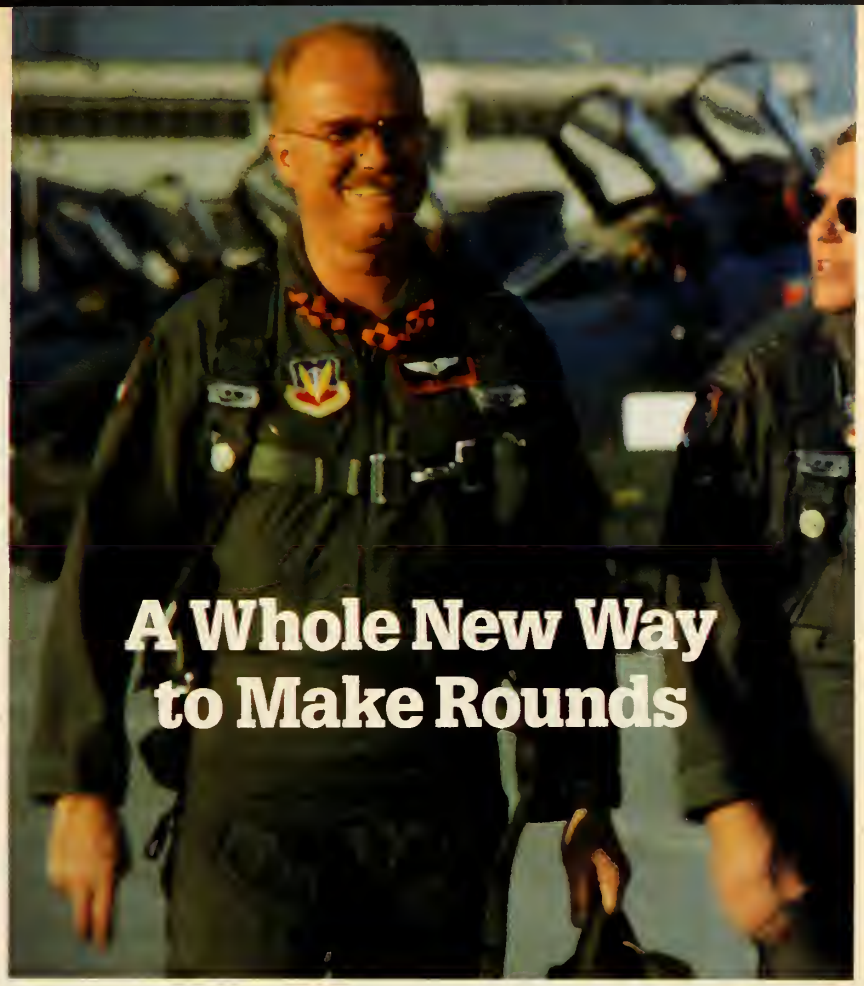

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From the Departments of Pediatrics and Pathology, University of Utah School of Medicine, Salt Lake City. Dr Smith is currently affiliated with the Department of Foods and Nutrition, Purdue University, West Lafayette, Indiana.

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WILLIAM G. RECTOR, Jr, MD; SUGANTHA GOVINDARAJAN, MD; KENT A. PENLEY; and FRANKLYN N. JUDSON, MD

From the Department of Medicine, Division of Gastroenterology, Denver General Hospital; the Rancho Los Amigos-University of Southern California Liver Unit, Downey, California; the Disease Control Service, Denver Department of Health and Hospitals; and the Department of Medicine, Division of Infectious Disease, University of Colorado Health Sciences Center, Denver.

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From the Division of Medical Oncology, University of Colorado Health Sciences Center, Denver.

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KENNETH G. JORDAN, MD

From the Department of Internal Medicine, Section of Neurology, Loma Linda University School of Medicine, Loma Linda, California.

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An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

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Discussant: NORA F. GOLDSCHLAGER, MD

A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine.

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Anesthesiology

Items of progress in anesthesiology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

74 **Regional Anesthesia in Children**

ELLIOT J. KRANE, MD, and DONALD C. TYLER, MD

75 **Continuous Noninvasive Arterial Monitoring**

CAROLYN SALTER, MD

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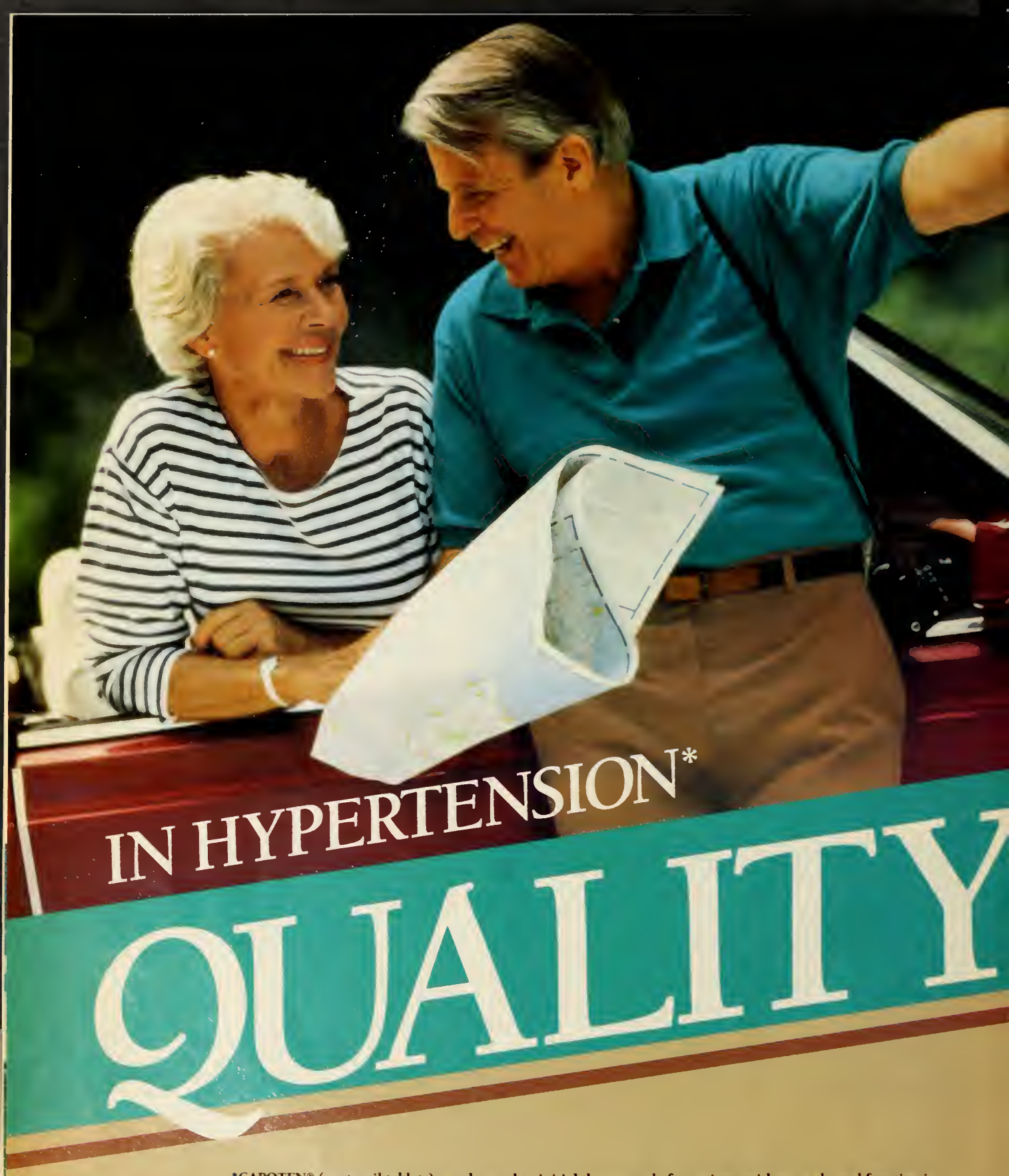

***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

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1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
2. Data on file, University of Connecticut.

SQUIBB

Means a feeling of well-being.

Well-being—a feeling difficult to describe when it's present; easy to spot when it's gone. CAPOTEN improved hypertensive patients' sense of general well-being.[1] CAPOTEN had a positive effect on patients' vitality and general health. In fact, all measures of well-being studied showed a trend toward improvement.[2]

These data are based on a multicenter, randomized, 24-week study of 626 mild-to-moderate hypertensive male patients with normal renal function, 181 of whom received captopril.

CAPOTEN—things are looking up for patients who need to keep their blood pressure down.

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Captopril Tablets

INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine > 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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ARMY RESERVE MEDICAL PROFILE NO. 4

ROBERT CHEONG LIM, J.R., M.D.

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Chief, Vascular Surgery Service, San Francisco General Hospital

Consultant, Letterman Army Medical Center

Colonel, U.S. Army Reserve

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RESIDENCY University of California School of Medicine.

FELLOWSHIPS NIH Fellowship in Vascular Surgery, V.A. Hospital, San Francisco; National Heart Institute Special Fellowship in Thromboembolic Diseases and Microcirculation, University of Gothenburg, Sweden.

OUTSTANDING ACHIEVEMENTS Joe Shoong Fellowship; Earl Hamilton Cornell Scholarship in Medicine; Ligature Order (Sweden); Alpha Omega Alpha; Distinguished Service Award, Youth Opportunity Program, HEW; Special Consultant, Special Project Office on Emergency Medical Services, HEW; Chinese-American Physicians Society; Who's Who in America.

"My professional career is devoted to patient care, teaching and research. Because of my special interest in the field of trauma surgery, I feel especially close to the work being done at Army medical centers such as Letterman Army Medical Center in San Francisco. I am particularly impressed with what they are doing to prepare young Army surgeons in dealing with trauma injuries.

"I joined the Army Reserve because I personally wanted to become more involved with military medicine at Letterman. It has a superior training program, and the quality of military medicine practiced is outstanding. The excellent care patients receive at Army medical facilities is up-to-date and surpasses the standard of care in many means. By being part of that team, I can provide the necessary backup, if needed, in a national emergency.

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†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

1419H8

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BRIEF SUMMARY
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg and 120 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission.

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes, however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%).

Cardiovascular	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia, congestive heart failure, flushing, hypotension, palpitations, syncope
Nervous System	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor
Gastrointestinal	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH (see hepatic warnings), vomiting, weight increase
Dermatologic	Petechiae, pruritus, photosensitivity, urticaria
Other	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use Information before prescribing

References: 1. Schroeder JS. Mod Med 1982;50(Sept):94-116. **2.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **3.** O'Rourke RA. Am J Cardiol 1985;56:34H-40H. **4.** McCall D, Walsh RA, Frohlich ED, et al. Curr Probl Cardiol 1985;10(8):6-80. **5.** Frishman WH, Charlap S, Goldberger J, et al. Am J Cardiol 1985;56:41H-46H. **6.** Shapiro W. Consultant 1984;24(Dec):150-159. **7.** O'Hara MJ, Khurmi NS, Bowles MJ, et al. Am J Cardiol 1984;54:477-481. **8.** Strauss WE, McIntyre KM, Parisi AF, et al. Am J Cardiol 1982;49:560-566. **9.** Feldman RL, Pepine CJ, Whittle J, et al. Am J Cardiol 1982;49:554-559.

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...without impairing psychomotor function in most patients*[2]
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*Because the effects of BuSpar in any individual patient may not be predictable, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.

For Brief Summary, please see following page.

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BuSpar® (buspirone HCl)

References: 1. Newton RE, *et al* A review of the side effect profile of buspirone. *Am J Med* 1986;80(3B):17-21 2. Moskowitz H and Smiley A Effects of chronically administered buspirone and diazepam on driving-related skills performance *J Clin Psychiatry* 1982;43(12,Sec 2) 45-55 3. Lader M Assessing the potential for buspirone dependence or abuse and effects of its withdrawal *Am J Med* 1987;82(5A):20-26

Contraindications: Hypersensitivity to buspirone.

Warnings: The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. Since blood pressure has become elevated when BuSpar was administered concomitantly with an MAOI, such concomitant use is not recommended. BuSpar should not be employed in lieu of appropriate antipsychotic treatment.

Precautions: ***General***—*Interference with cognitive and motor performance:* Although buspirone is less sedating than other anxiolytics and does not produce significant functional impairment, its CNS effects in a given patient may not be predictable; therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone does not affect them adversely. Although buspirone has not been shown to increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use with alcohol.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug dependent patients: Because buspirone will not block the withdrawal syndrome often seen with cessation of therapy with benzodiazepines and other common sedative/hypnotic drugs, before starting buspirone withdraw patients gradually from their prior treatment, especially those who used a CNS depressant chronically. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its elimination half-life. The withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors: Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported, the syndrome may be due to increased central noradrenergic activity or may be attributable to dopaminergic effects (ie, represent akathisia).

Information for Patients—Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions—Concomitant use with other CNS active drugs should be approached with caution (see **Warnings**). Concomitant use with trazodone may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. Buspirone does not displace tightly bound drugs like phenytoin, propranolol, and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility—No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy: Teratogenic Effects—Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers—Administration to nursing women should be avoided if clinically possible.

Pediatric Use—The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly—No unusual, adverse, age-related phenomena have been identified in elderly patients receiving a total, modal daily dose of 15 mg.

Use in Patients with Impaired Hepatic or Renal Function—Since buspirone is metabolized by the liver and excreted by the kidneys, it is not recommended in severe hepatic or renal impairment.

Adverse Reactions (See also Precautions): ***Commonly Observed***—The more commonly observed untoward events include dizziness, nausea, headache, nervousness, lightheadedness, and excitement.

Associated with Discontinuation of Treatment—The more common events causing discontinuation included: central nervous system disturbances (3.4%), primarily dizziness, insomnia, nervousness, drowsiness, lightheaded feeling, gastrointestinal disturbances (1.2%), primarily nausea; miscellaneous disturbances (1.1%), primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary

Incidence in Controlled Clinical Trials—Adverse events reported by 1% or more of 477 patients who received buspirone in four-week, controlled trials: *Cardiovascular:* Tachycardia/palpitations 1%. *CNS:* Dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, lightheadedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. *EENT:* Blurred vision 2%. *Gastrointestinal:* Nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. *Musculoskeletal:* Musculoskeletal aches/pains 1%. *Neurological:* Numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. *Skin:* Skin rash 1%. *Miscellaneous:* Headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-marketing Evaluation—The relative frequency of all other undesirable events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under well-controlled, open, and uncontrolled conditions is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. *Cardiovascular*—frequent: nonspecific chest pain; infrequent: syncope, hypotension, hypertension; rare: cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy, bradycardia. *Central Nervous System*—frequent: dream disturbances, infrequent: depersonalization, dysphoria, noise intolerance, euphoria, akathisia, tearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation, seizures; rare: feelings of claustrophobia, cold intolerance, stupor, slurred speech, psychosis. *EENT*—frequent: tinnitus, sore throat, nasal congestion; infrequent: redness and itching of the eyes, altered taste, altered smell, conjunctivitis; rare: inner ear abnormality, eye pain, photophobia, pressure on eyes. *Endocrine*—rare: galactorrhea, thyroid abnormality. *Gastrointestinal*—infrequent: flatulence, anorexia, increased appetite, salivation, irritable colon, rectal bleeding, rare: burning of the tongue. *Genitourinary*—infrequent: urinary frequency, urinary hesitancy, menstrual irregularity and spotting, dysuria; rare: amenorrhea, pelvic inflammatory disease, enuresis, nocturia. *Musculoskeletal*—infrequent: muscle cramps, muscle spasms, rigid/stiff muscles, arthralgias. *Neurological*—infrequent: involuntary movements, slowed reaction time; rare: muscle weakness. *Respiratory*—infrequent: hyperventilation, shortness of breath, chest congestion; rare: epistaxis. *Sexual Function*—infrequent: decreased or increased libido; rare: delayed ejaculation, impotence. *Skin*—infrequent: edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema, blisters; rare: acne, thinning of nails. *Clinical Laboratory*—infrequent: increases in hepatic aminotransferases (SGOT, SGPT); rare: eosinophilia, leukopenia, thrombocytopenia. *Miscellaneous*—infrequent: weight gain, fever, roaring sensation in the head, weight loss, malaise; rare: alcohol abuse, bleeding disturbance, loss of voice, hiccoughs.

Drug Abuse and Dependence: ***Controlled Substance Class***—Not a controlled substance.

Physical and Psychological Dependence—Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Overdosage: ***Signs and Symptoms***—At doses approaching 375 mg/day the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress. No deaths have been reported in humans either with deliberate or accidental overdosage.

Recommended Overdose Treatment—General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceuticals Representative.

U.S. Patent Nos. 3,717,634 and 4,182,763

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

MOLECULAR GENETICS IN MEDICINE—Vol 7 in Progress in Medical Genetics—Edited by Barton Childs, MD, Professor Emeritus; Neil A. Holtzman, MD, Professor; Haig H. Kazazian, Jr, MD, Professor; and David L. Valle, MD, Professor, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore. Elsevier, 52 Vanderbilt Ave, New York, NY 10017, 1987. 245 pages, $45.

MONITORING AND EVALUATION—ANESTHESIA SERVICES. Joint Commission on Accreditation of Healthcare Organizations, 875 N Michigan Ave, Chicago, IL 60611, 1987. 56 pages, $30 (paperback).

MONITORING AND EVALUATION—PHYSICAL REHABILITATION SERVICES. Joint Commission on Accreditation of Healthcare Organizations, 875 N Michigan Ave, Chicago, IL 60611, 1988. 68 pages, $30 (paperback).

MONITORING AND EVALUATION OF THE QUALITY AND APPROPRIATENESS OF CARE—A HOME CARE EXAMPLE. Joint Commission on Accreditation of Healthcare Organizations, 875 N Michigan Ave, Chicago, IL 60611, 1988. 21 pages, $5 (paperback).

OCCUPATIONAL BACK PAIN—Vol. 2, No. 1 of SPINE: STATE OF THE ART REVIEWS—Edited by Richard A. Deyo, MD, MPH, Director, Health Services Research and Development, Seattle Veterans Administration Medical Center, and Associate Professor, Department of Medicine and of Health Services, University of Washington School of Medicine, Seattle. Hanley & Belfus, Inc, 210 S 13th St, Philadelphia, PA 19107, 1987. 165 pages; $32 (single issue), $75 (subscription, 3 issues per year).

OCULOPLASTIC, ORBITAL, AND RECONSTRUCTIVE SURGERY—Volume One—EYELIDS—Edited by Albert Hornblass, MD, Clinical Professor of Ophthalmology, State University of New York, Health Science Center at Brooklyn, and Director of Ophthalmic Plastic, Orbital and Reconstructive Surgery, Manhattan Eye, Ear and Throat Hospital; Lenox Hill Hospital; and State University of New York Health Science Center at Brooklyn. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1988. 703 pages, $125.

QUALITY AND HOME HEALTH CARE—REDEFINING THE TRADITION. Joint Commission on Accreditation of Healthcare Organizations, 1987. 127 pages, $30 (paperback).

THE SHOULDER—Edited by Carter R. Rowe, MD, Associate Clinical Professor (Emeritus), Department of Orthopaedic Surgery, Harvard Medical School, and Senior Surgeon, Department of Orthopaedics, Massachusetts General Hospital, Boston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 654 pages, $140.

SICKLE CELL ANEMIA AND THALASSEMIA—A PRIMER FOR HEALTH CARE PROFESSIONALS—R. G. Huntsman, MD (Cantab), FRCP (UK), Medical Director, Canadian Sickle Cell Society and Canadian Red Cross Blood Transfusion Service, and Professor of Pathology (Hematology), Memorial University of Newfoundland. Canadian Sickle Cell Society, PO Box 13156, Station A, St John's, Newfoundland, Canada A1B 4A4, 1987. 204 pages, $10 (paperback).

TEMPORARY CARDIAC PACING—Carl E. Bartecchi, MD, Clinical Professor, Departments of Medicine and Family Medicine, University of Colorado School of Medicine. Precept Press, 160 E Illinois St, Chicago, IL 60611, 1987. 212 pages, $45 (clothbound).

THE TRAGEDY OF BLACK LUNG—FEDERAL COMPENSATION FOR OCCUPATIONAL DISEASE—Peter S. Barth, Professor of Economics, University of Connecticut, and formerly Executive Director, National Commission on State Workmen's Compensation Laws. W. E. Upjohn Institute for Employment Research, 300 S Westnedge Ave, Kalamazoo, MI 49007, 1987. 285 pages, $11.95 (paperback), $16.95 (cloth).

UROLOGY—Problems in Primary Care Series—Edited by Elroy D. Kursh, MD, Associate Professor of Surgery/Urology, and Martin I. Resnick, MD, Professor and Chairman, Division of Urology, Case Western Reserve University School of Medicine, Cleveland. Medical Economics Books, Oradell, NJ 07649, 1987. 322 pages, $32.95 (softbound).

WRONG DIAGNOSIS—WRONG TREATMENT—THE PLIGHT OF THE ALCOHOLIC IN AMERICA—Joseph D. Beasley, MD, Medical Director, Brunswick House, Amityville, Long Island, New York. Creative Infomatics, Inc, PO Box 1607, Durant, OK 74702-1607, 1987. 268 pages, $12.95 (paperback).

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150 mg tablets bid

1. Sontag S, Robinson M, McCallum RW, et al: Ranitidine therapy for gastroesophageal reflux disease: Results of a large double-blind trial. *Arch Intern Med* 1987;147:1485-1491

Please see next page for Brief Summary of Prescribing Information.

Glaxo/ ROCHE

ZANTAC® 150 Tablets **BRIEF SUMMARY**
(ranitidine hydrochloride)

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.
INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis)
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.
In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.
CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.
PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.
Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.
Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.
In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.
Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established.
Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.
ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.
Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.
Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.
Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.
Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.
Musculoskeletal: Rare reports of arthralgias.
Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.
Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.
OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.
DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.
Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.
GERD: The current recommended adult oral dosage is 150 mg twice a day.
Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.
HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).
ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).
Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Glaxo May 1988

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The World's Most Popular K

For good reasons

- ☐ **It works**—a 12-year record of efficacy[1]
- ☐ **It's safe**—unsurpassed by any other KCl tablet or capsule[2]*
- ☐ **It's acceptable vs liquids**—greater palatability, fewer GI complaints, lower incidence of nausea[2]
- ☐ **It's comparable to 10 mEq**—in low-dosage supplementation[3]†
- ☐ **It's economical**—less expensive than all other leading KCl slow-release supplements on a per tablet cost to the patient[1]

Slow-K®
potassium chloride
slow-release tablets 8 mEq (600 mg)

For patients who can't or won't tolerate liquid KCl.

*The most common adverse reactions to potassium salts are gastrointestinal side effects.

†Pooled mean serum potassium following oral administration of 30 mEq K-Tab compared to 24 mEq Slow-K in diuretic-treated hypertensives (n = 20) over 8 weeks.

C I B A

References: 1. Data on file, CIBA Pharmaceutical Company. 2. Skoutakis VA, Acchiardo SR, Wojciechowski NJ, et al. Liquid and solid potassium chloride: Bioavailability and safety. *Pharmacotherapy* 1980;4(6):392-397. 3. Skoutakis VA, Carter CA, Acchiardo SR: Therapeutic assessment of Slow-K and K-Tab potassium chloride formulations in hypertensive patients treated with thiazide diuretics. *Drug Intell Clin Pharm* 1987;21:436-440.

Slow-K®
potassium chloride USP
Slow-Release Tablets
8 mEq (600 mg)

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION SEE PACKAGE INSERT)

INDICATIONS AND USAGE
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.
1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy; and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.
CONTRAINDICATIONS
Potassium supplements are contraindicated in patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene) (see OVERDOSAGE).
All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation. Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to an enlarged left atrium.
WARNINGS
Hyperkalemia (See OVERDOSAGE).
In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic.
The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.
Interaction With Potassium-Sparing Diuretics
Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.
Gastrointestinal Lesions
Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains approximately one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.
Metabolic Acidosis
Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.
PRECAUTIONS
General:
The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium.
Information for Patients
Physicians should consider reminding the patient of the following:
To take each dose without crushing, chewing, or sucking the tablets.
To take this medicine only as directed. This is especially important if the patient is also taking both diuretics and digitalis preparations.
To check with the physician if there is trouble swallowing tablets or if the tablets seem to stick in the throat.
To check with the doctor at once if tarry stools or other evidence of gastrointestinal bleeding is noticed.
Laboratory Tests
Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.
Drug Interactions
Potassium-sparing diuretics: see WARNINGS.
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term carcinogenicity studies in animals have not been performed.
Pregnancy Category C
Animal reproduction studies have not been conducted with Slow-K. It is also not known whether Slow-K can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Slow-K should be given to a pregnant woman only if clearly needed.
Nursing Mothers
The normal potassium ion content of human milk is about 13 mEq/L. It is not known if Slow-K has an effect on this content. Caution should be exercised when Slow-K is administered to a nursing woman.
Pediatric Use
Safety and effectiveness in children have not been established.
ADVERSE REACTIONS
One of the most severe adverse effects is hyperkalemia (see CONTRAINDICATIONS, WARNINGS, and OVERDOSAGE). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see CONTRAINDICATIONS and WARNINGS); other factors known to be associated with such conditions were present in many of these patients.
The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.
Skin rash has been reported rarely.
OVERDOSAGE
The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see CONTRAINDICATIONS and WARNINGS). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration (6.5-8.0 mEq/L) and characteristic electrocardiographic changes (peaking of T waves, loss of P wave, depression of S-T segment, and prolongation of the Q-T interval). Late manifestations include muscle paralysis and cardiovascular collapse from cardiac arrest (9-12 mEq/L).
Treatment measures for hyperkalemia include the following: (1) elimination of foods and medications containing potassium and of potassium-sparing diuretics; (2) intravenous administration of 300-500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml; (3) correction of acidosis, if present, with intravenous sodium bicarbonate; (4) use of exchange resins, hemodialysis, or peritoneal dialysis.
In treating hyperkalemia in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.
DOSAGE AND ADMINISTRATION
The usual dietary intake of potassium by the average adult is 40-80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires the loss of 200 or more mEq of potassium from the total body store. Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for the prevention of hypokalemia to 40-100 mEq or more per day for the treatment of potassium depletion. Large numbers of tablets should be given in divided doses.
Note: Slow-K slow-release tablets must be swallowed whole and never crushed, chewed, or sucked.
HOW SUPPLIED
Tablets—600 mg of potassium chloride (equivalent to 8 mEq) round, buff colored, sugar-coated (imprinted Slow-K)
Bottles of 100 . . . . . NDC 0083-0165-30
Bottles of 1000 . . . . . NDC 0083-0165-40
Consumer Pack—One Unit
12 Bottles—100 tablets each . . . . . NDC 0083-0165-65
Accu-Pak® Unit Dose (Blister pack)
Box of 100 (strips of 10) . . . . . NDC 0083-0165-32
Do not store above 86°F (30°C). Protect from moisture. Protect from light.

Dispense in tight, light-resistant container (USP).

Dist. by:
CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901
C87-31 (Rev. 8/87)

C I B A

128-3568-A

THE INSIDE STORY
IN HYPERTENSION

PEEL

PEEL

PEEL

TRANDATE® *bid*

labetalol HCl/Glaxo 100 mg tablets

Because it vasodilates

THE OUTSIDE STORY

UNCOMPROMISED VITALITY

- ☐ Low incidence of fatigue and impotence[7]
- ☐ Preserves exercise tolerance[5]
- ☐ High level of patient acceptance

Trandate Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

For references and a complete listing of reported adverse reactions, including incidence at various dosage levels, please see ADVERSE REACTIONS section of the Brief Summary of Prescribing Information on next page.

Please see next page for references and Brief Summary of Prescribing Information.

Effective blood pressure control

TRANDATE® *bid*

labetalol HCl/Glaxo 100 mg tablets

Because it vasodilates

References: 1. Malini PL, Strocchi E, Negroni S, et al: Renal haemodynamics after chronic treatment with labetalol and propranolol. *Br J Clin Pharmacol* 1982;13(suppl 1):123S-126S. 2. Pedersen EB, Larsen JS: Effect of propranolol and labetalol on renal haemodynamics at rest and during exercise in essential hypertension. *Postgrad Med J* 1980;56(suppl 2):27-32. 3. Wallin JD: Antihypertensives and their impact on renal function. *Am J Med* 1983;75:103-108. 4. Koch G: Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol. *Br Heart J* 1979;41(2):192-198. 5. Feit A, Holtzman R, Cohen M, et al: Effect of labetalol on exercise tolerance and double product in mild to moderate essential hypertension. *Am J Med* 1985;78:937-941. 6. Lund-Johansen P: Short- and long-term (six-year) hemodynamic effects of labetalol in essential hypertension. *Am J Med* 1983;75:24-31. 7. Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:285-293.

TRANDATE® Tablets **BRIEF SUMMARY**
(labetalol hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy before major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see PRECAUTIONS: Drug Interactions).

PRECAUTIONS: General: *Impaired Hepatic Function:* TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will

TRANDATE® Tablets (labetalol hydrochloride)

be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multicenter, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, headache. ***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, taste distortion. ***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, drowsiness. ***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, increased sweating. ***Cardiovascular:*** Edema, postural hypotension. ***Respiratory:*** Dyspnea. ***Skin:*** Rash. ***Special Senses:*** Vision abnormality, vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including, rarely, syncope. ***Central and Peripheral Nervous Systems:*** Paresthesia, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment. ***Collagen Disorders:*** Systemic lupus erythematosus; positive antinuclear factor (ANF). ***Eyes:*** Dry eyes. ***Immunological System:*** Antimitochondrial antibodies. ***Liver and Biliary System:*** Cholestasis with or without jaundice. ***Musculoskeletal System:*** Muscle cramps, toxic myopathy. ***Respiratory System:*** Bronchospasm. ***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia. ***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents. ***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on psychometrics. ***Cardiovascular:*** Intensification of AV block (see CONTRAINDICATIONS). ***Allergic:*** Fever combined with aching and sore throat; laryngospasm, respiratory distress. ***Hematologic:*** Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. ***Gastrointestinal:*** Mesenteric artery thrombosis, ischemic colitis. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

April 1988

Glaxo

Glaxo Inc., Research Triangle Park, NC 27709

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

July 29-30—**Coconino County Medical Society's Summer Medical Seminar.** Little America Hotel, Flagstaff. Fri-Sat. Contact: Coconino County Medical Society, (602) 774-1886.

October 21-23—**Diagnosis and Management of Respiratory Diseases.** The Boulders, Scottsdale. Fri-Sun. Contact: Medical Education Resources, 1 (800) 421-3756.

November 11-13—**17th Annual Seminar—Musculoskeletal Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Department of Radiology, Maricopa Medical Center, (602) 267-5361.

December 3-4—**Annual Meeting of the Arizona Chapter of the American College of Surgeons.** Rancho de los Caballeros, Wickenburg. Sat-Sun. Contact: Lee Ansel, MD, Program Chairman, (602) 251-3131.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

October 14—**18th Course on Allergy and Immunology.** Pacific Presbyterian Medical Center at San Francisco. Fri. Contact: Herbert S. Kaufman, MD, PPMC, 2340 Clay St, Rm 313, San Francisco 94115. (415) 923-3441.

ANESTHESIOLOGY

August 21-27—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Inter-Continental Hotel, Wailea, Maui. Sun-Sat. 20 hrs. $325/$375. Contact: CSA, 1065 E. Hilldale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 30-October 1—**Anesthesia Practice 1988.** Anesthesiology Educational Foundation. Fri-Sun. 11 hrs. Contact: AEF, PO Box 24230, Federal Building, Los Angeles 90024. (213) 825-0736.

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologist at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 29-February 3—**Clinical Update in Anesthesiology.** Tucson Hospitals Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray G. Atnikov, MD, c/o Box F110-63, Blaine, WA 98230. (604) 874-5291.

CARDIOLOGY

July 22-23—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. $295. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 34)

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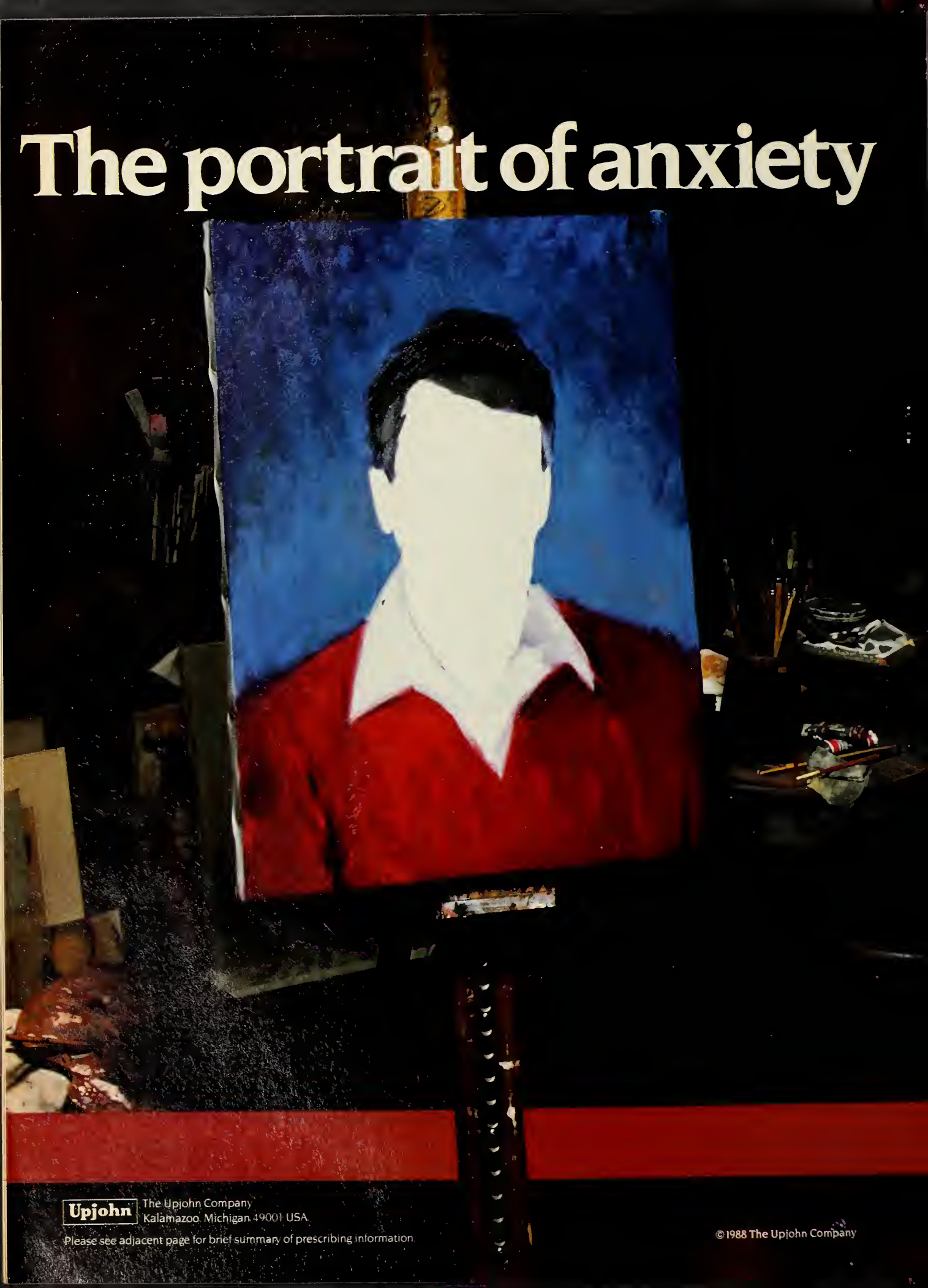
For All the Commitments You Make®

The portrait of anxiety



Upjohn The Upjohn Company
Kalamazoo, Michigan 49001 USA

Please see adjacent page for brief summary of prescribing information.

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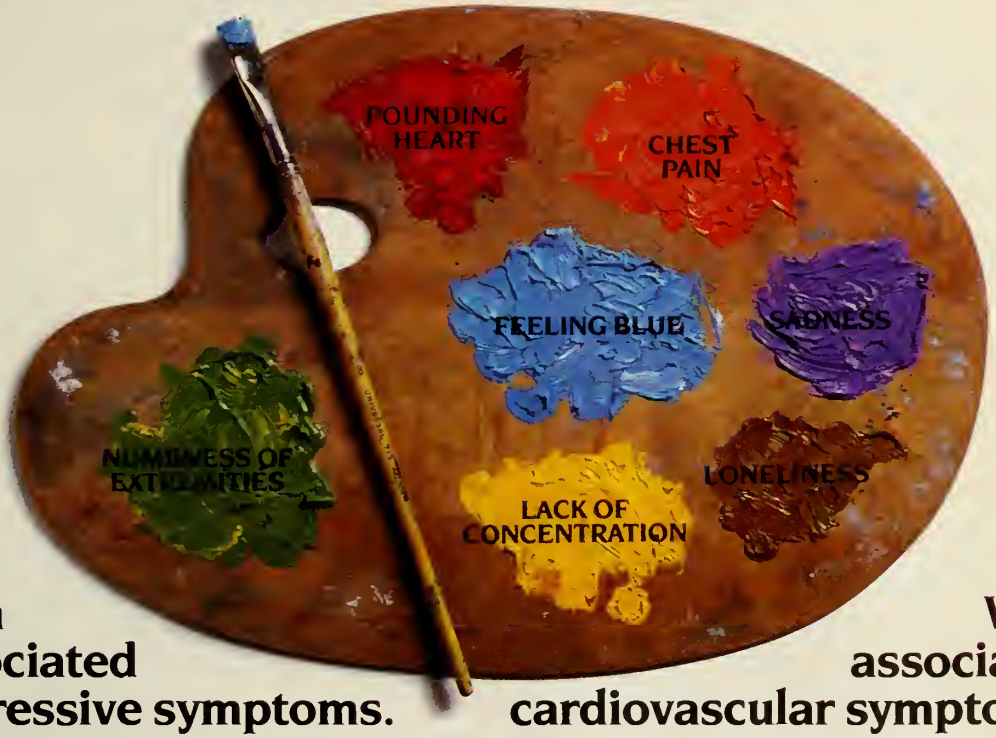
is often complicated



With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax®

alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) C

INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma.

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

Upjohn THE UPJOHN COMPANY J-9135
Kalamazoo, Michigan 49001, USA April 1988

CONTINUING MEDICAL EDUCATION

(Continued from Page 30)

July 31-August 5—**Current Concepts in Cardiology: 1988.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 18 hrs. $395. Contact: UCD.

August 4-6—**Critical Care Cardiology.** American College of Cardiology at Fairmont Hotel, San Francisco. Thurs-Sat. 17 hrs. $375. Contact: ACC Extramural Programs, Dept 5080, Washington, DC 20061-5080. (800) 253-4636.

August 25-26—**Advanced Fetal Heart Rate Monitoring.** Center for Health Education at Red Lion Resort, Santa Barbara. Thurs-Fri. Contact: The Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801.

October 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hyatt on Union Square, San Francisco. Fri-Sat. $295. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

August 12-14—**Dermatologic Surgery: State of the Art 1988.** Stanford University at Monterey Sheraton, Monterey. Fri-Sun. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, UMC Stanford, 94305. (415) 723-6105.

August 21-28—**International Symposium: Hot Spots in Dermatology.** Kauai Medical Group at Molokai, Hawaii. One week. Contact: David Elpern, MD, 3420-B Kuhio Highway, Lihue, Hawaii 96766. (808) 245-1507.

EMERGENCY MEDICINE

July 22-24—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

August 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II & Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

August 29-September 2—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

October 10-14—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium I & Optional Advanced Emergency Procedures Laboratory.** UCSD at Catamaran Resort Hotel, San Diego. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 21-23—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

November 4-6—**Management of the Child With Head Injury.** Children's Hospital Oakland at Monterey Conference Center and Hotel Pacific, Monterey. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, Continuing Medical Education, Children's Hospital Oakland, 747-52nd St, Oakland 94609. (415) 428-3021.

November 14-18—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III & Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 4-9—**Current Concepts in Emergency Care.** Institute for Emergency Medical Education at Royal Lahaina Resort, Maui, Hawaii. Sun-Fri. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. (800) 524-5264.

December 5-9—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II & Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

January 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. $450. Contact: UCSD.

January 27-29—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

(Continued on Page 118)

A NEW H_2 Antagonist

AXID® 300mg

nizatidine

Effective once-nightly
duodenal ulcer therapy available in a

Unique Convenience Pak

for better patient compliance

AXID®
nizatidine capsules

Brief Summary. Consult the package insert for prescribing information.

Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg h.s. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions—No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement compared to concurrent controls, and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay.

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating rats. Pups reared by treated lactating rats had depressed growth rates. Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported, it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported.

Overdosage: There is little clinical experience with overdosage of Axid in humans. If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous LD_{50} values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively. PV 2091 AMP [041288]

Axid® (nizatidine, Lilly)

Lilly

Eli Lilly and Company
Indianapolis, Indiana
46285

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A better alternative for hypertensives who are going bananas...

Spare your patients the extra cost—in calories, sodium and dollars.

Spare your patients the rigors of dietary K^+ supplementation.

DYAZIDE®

25mg Hydrochlorothiazide/**50mg** Triamterene/SKF

Effective antihypertensive* therapy...without the bananas

DAW
'DYAZIDE' AS WRITTEN.

* Not for initial therapy. See brief summary.

Before prescribing, see complete prescribing information in SK&F CO. literature or PDR. The following is a brief summary.

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.
Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is intracellular in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.
Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin(ACTH)). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.
Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.
Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BRS-DZ-L45

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Cidra, P.R. 00639

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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

JULY 1988, VOL. XLV, NO. 7

Peripheral Vision

Marshall B. Block, M.D.

One evening I received an urgent phone call from my father, Charles. It seems that while he was driving his automobile in downtown Miami, the car that he was driving, for some reason, began speeding close to 60 m.p.h. He avoided several pedestrians and several parked cars, thankfully, but in order to stop he swerved into an alley and rammed the car into a large metal garbage container. Having heard of several recent automobile recalls because of spontaneous acceleration problems, I asked what year automobile he was driving. He stated, "I don't think it had anything to do with the car, I think I had my foot on the gas pedal instead of the brake. Maybe I'm too old to drive anymore." However, my mother, always young at heart, wouldn't let him get off so easily. "He always wanted to be older than he was; when he was 69 he kept telling everyone he was going to be 70. His problem is that when he drives he is always looking to the side and never looking straight ahead where he should be. If he would just look straight ahead, he wouldn't have any problems." Unfortunately, the same is not true for us.

It would appear that everywhere we turn, we find "menacing" faces attempting to impinge on our ability to practice medicine. In-hospital review by Quality Assurance programs (tumor boards, mortality and morbidity committees), and outside reviewers, both public (PRO) and private (HMOs, IPAs, PPOs, etc.) is now a fact of life. Expansion of these activities in the outpatient arena with oversight of outpatient surgical facilities, extended care facilities ("nursing homes") and ultimately our outpatient ambulatory care centers ("our offices"). These reviews ostensibly are for medical necessity, but as a side-light (perhaps appropriately) they highlight quality of care issues, and as such, serve an additional function of exposing inappropriate medical care when it occurs. With this amount of scrutiny, it is little wonder that litigious actions are increasing. We, thus, are faced not only with possible professional challenges (necessity and quality), but in addition, may face personal punitive damages. The idea of only "bad doctors getting sued" is obsolete.

"Good" doctors are sued daily for activities which may not be a reflection of their personal medical competence, although on occasion it does happen, as we all are human and do make errors. Rather, as I prefer to call it, mistakes can be made in the "system" which can result in inappropriate decisions which ultimately result in physicians bearing the responsibility for such errors. As an example, a physician orders a test but the result never returns to his desk. The patient never calls for the result, assuming by the lack of contact from the physician that it was normal. Unfortunately, the test was abnormal and the patient suffers an ill-effect while the diagnosis was delayed. Our system is composed of a complex network of people and paper interactions which can, and does break down at times. Can a physician remember every test that is ordered? Can a system be developed to track every test and result, and be sure all are done correctly, and reported appropriately? Who is going to pay for the personnel and computers and time necessary to develop such a system in each individual physician's office? These are questions which need answers now. I believe it is possible to resolve some of these potential problem areas. Physicians interested in such activity should be sought and their skills harnessed to develop systems which can be used by physicians and their offices. Perhaps, MICA could spearhead such an effort.

Perhaps my mother is right, that if we look straight ahead we may not be distracted. On the other hand, peripheral vision sometimes gives us a perspective that enhances our primary mission. In this regard, I believe that we need to look out the side and develop systems that allow us to continue providing the best medical care available. If we need the help of others to accomplish it, so be it. That should not deter us.

I suspect that my father has gotten more out of life by looking out to the side, from time to time, than looking just straight ahead. ❑

Marshall B. Block, M.D., Editor

JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

JULY 1988, VOL. XLV, NO. 7

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- Electronic Information for Physicians
- Dean's Cultural Rounds
- New Active Members
- Physicians In The News
- Utah Guest Editorial
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From Our President

Richard L. Collins, M.D.

One of the most devastating experiences physicians face is the process of being sued.

The stress associated with the process has destroyed families, professional relationships and even careers. Even if physicians manage to keep it all together, many feel betrayed, isolated and embarrassed.

Until recently, there has been nowhere to turn for any kind of peer support, primarily because lawyers and representatives of insurance companies instruct sued physicians not to discuss their case with anyone.

But now, under the aegis of the ArMA Committee on Professional Affairs, a new subcommittee has been organized to help physicians cope with this ever-more-common process. Established at the joint urging of the Arizona Chapter of the American College of Obstetrics and Gynecology and the Phoenix OB-GYN Society, the committee is made up of physicians who personally have been through the liability lawsuit process and know the pressures and problems involved.

To provide assistance to colleagues facing the same trauma, the Peer Support Subcommittee has established several basic goals:

* To reach physicians being sued so that support can be offered: Because physicians facing litigation are either embarrassed to admit they are being sued or have been instructed not to discuss the case – or both – it is difficult to identify physicians who might need the support of knowing they are not alone in the turmoil of emotion and stress they are experiencing. Committee members hope that information disseminated about the subcommittee's establishment will encourage physicians to contact the peer support group.

* To provide emotional support to help physicians handle the stress they experience during the litigation process: Because the emotional and psychological pressures resulting from the process of being sued are so intense, many physicians experience serious interpersonal problems. The support group hopes to help physicians focus on personal priorities – to remember what's really important in an individual's life – instead of allowing lawsuit-related stress to damage or destroy personal or professional relationships.

* To provide technical information about the litigation process itself, including the perils and pitfalls of its various parts: Because attorneys sometimes fail to properly prepare their physician clients for the various events which affect trial outcomes, physicians sometimes have not done as well as the facts of their cases would merit. Physicians often aren't told how important it is to be prepared for a deposition; what a critically important role it plays in court, enhancing or destroying the physician's credibility. But almost all the peer support subcommittee members have experienced the process, can share its hazards, and let their colleagues know how best to prepare themselves for both depositions and trial testimony.

None of the above goals are specific to any individual lawsuit, nor could they detrimentally affect the outcome of any specific trial. The committee hopes this approach will help overcome the prohibitions voiced by attorneys and insurance company representatives. (Continued on page 17)

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Electronic Information For Physicians: A New Dimension In Solving Traditional Problems Part I

Physicians have a continual need for information. This is a natural consequence of the overwhelming and increasing quantity of biomedical knowledge required for the practice of medicine today. Traditional sources of this information include colleagues, books, and journals, both in the hospital and office environment. Thanks in part to the decreasing cost of computer equipment, a new, low-cost, more up-to-date source of information is now readily available to physicians: electronic information. This information may often be more convenient, more current, and more relevant than traditional sources. This article provides some examples of the types of electronic information which can be useful in addressing physician information needs. It focuses on AMA/NET, the AMA sponsored nationwide medical information network which is now available to physicians throughout the U.S.

I. The Diagnostic Problem

Probably the most common problem that physicians face is making a diagnosis. In the overwhelming majority of cases, the signs and symptoms of a patient's presenting illness are clear and easily recognizable and the diagnosis is rapidly made. However there is a small percentage of cases which present puzzling combinations of findings. It is in these cases that physicians traditionally seek the help of colleagues, books and the recent literature. Colleagues, of course, are an excellent source of information. However, they are not always readily available. Books typically are limited in that their information is at least one year old, and is usually organized by disease, not signs and symptoms. Because of this, a diagnostic hypothesis must be formed before the information is accessible. Even books which focus on signs, symptoms, and differential diagnosis may not provide ready access to information relevant to a specific patient with an unusual combination of findings.

While the recent literature is more current than books, it is also organized by disease and is more difficult to access. Only a limited number of journals can be available in the physician's office. These will typically be organized chronologically, and finding information on a particular topic may be quite time consuming. A well organized and up-to-date reprint system may compensate for these problems somewhat.

The nearest medical library will undoubtedly have a much more comprehensive collection of journals and also more capabilities for locating relevant articles, for example using Index Medicus. However, the library may also not be very convenient for the physician.

How can electronic information help? AMA/NET provides two different types of information which can be of assistance in a diagnostic problem: 1) DxPlain, a diagnostic assistance program, and 2) various methods for searching and accessing the medical literature. The DxPlain system is unique to AMA/NET; it provides patient-specific diagnostic information. Upon entering DxPlain, information is requested regarding the age and sex of the patient, duration of the problem, and the signs, symptoms, and lab findings associated with this condition. This information is entered in a very natural form with opportunities for correcting spelling and other typographical errors. After entering all the information for the patient, DxPlain produces a list of diagnostic possibilities. This list is divided into common and rare diseases, and each disease shown is given a ranking according to the likelihood that it could be responsible for the observed patient signs and symptoms. DxPlain then will provide explanations describing those signs and symptoms that led to the inclusion of each diagnosis, other findings which are not explained, and additional findings which were not noted but would be expected in that particular condition. Thus, DxPlain can help the physician to both generate and "think through" the differential diagnosis in a puzzling case. It functions as a specialized, patient-specific differential diagnosis reference allowing rapid access to information which can be helpful in the diagnostic process.

Another important area where electronic information can be extremely useful is in search and retrieval of recent literature. AMA/NET provides several methods of accessing the medical literature. The first of these, is EMPIRES (Excerpta Medica Physicians Information Retrieval and Education Service), which indexes articles from 328 key clinical journals. Searching can be done in one of two ways: easy search and advanced search. In easy search, two keywords are entered and a search is performed for all references which pertain to both those keywords. An option is provided for restricting the search to the last six months. Very little (if any) knowledge with respect to searching techniques in databases is required to use easy search. In advanced search, as many keywords as desired may be entered, and combined in whatever way desired. Repeated searches can be done to narrow down the selections as needed. While advanced search is not difficult to use, it does require some knowledge of both searching techniques and the commands available. AMA/NET provides access to MEDLINE, the National Library of Medicine database of the world's biomedical literature, in two separate ways. First, access is provided by PaperChase, a friendly

user interface developed at the Beth Israel Hospital in Boston. This program allows the physician with very little searching experience or knowledge of computers to construct a successful search of some complexity. Many physicians have found that it provides a fast and easy way to access the medical literature.

The National Library of Medicine's own user interface for MEDLINE, Grateful Med, is also available on AMA/NET. It provides a slightly different environment for helping the physician to develop and execute an appropriate search.

All three of these methodologies provide a useful way to access the most recent medical literature. Although the full text of articles found is not on-line for immediate reading, abstracts are available for the majority of the articles. Also, it is possible to order paper copies of any articles retrieved (up to five EMPIRES articles per month are available at no charge).

II. The Therapeutic Problem

The physician's approach to a therapeutic problem is very similar to the diagnostic, although there are some sources of information which are more directly helpful. As with diagnostic problems, the traditional options available are colleagues, books, and literature. If information is desired on a specific drug or a class of drugs, this can be obtained from a number of references which are often readily available. However, the often-asked question regarding the determination of the currently accepted therapy for a given disease is sometimes more difficult. Here again, electronic access to the most recent literature can be very helpful.

One of the keywords allowed in literature searching is "review." This results in the ability to access a recent review article on any given condition. This can often result in rapid identification of currently acceptable therapy.

Another common therapeutic problem is assessing the possibility of drug interactions, especially for a patient on many different medications. The MEDICOM drug interaction database recently became available on AMA/NET. It allows entry and storage of specific patient drug profiles so that patients with difficult drug interaction problems can be easily reevaluated when therapy is changed. In addition to drug interactions, drug-food, drug-nutrient, and drug-disease, and potential allergic reactions are also reported. Each reaction has an associated level of severity. If desired, output can be limited to the most clinically significant reactions. This avoids one of the classic problems in consulting printed drug interaction references: namely, the hundreds of interactions listed which have no practical clinical significance.

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William A. Yasnoff, M.D., Ph.D.
American Medical Association

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Dean's Cultural Rounds

Medical education, patient care and research are demanding endeavors which take place in the highly technologic environment of the Arizona Health Sciences Center (AHSC). To balance this environment, we suggested to then Dean Kettel that a new sort of "rounds" be initiated. From this initiative the Dean's Cultural Rounds evolved, to take their place along with the established Dean's Clinical and Dean's Educational Rounds. These are collegial activities with wide appeal to all elements of AHSC.

The introduction of the humanities into medical milieu, the purpose of the Dean's Cultural Rounds, is not a luxury, but an essential component of our educational process. Artistic programs, such as vocal and instrumental performances and art exhibits constitute a powerful instrument for enrichment of the daily working lives of the students, resident physicians, faculty and staff.

The Dean's Cultural Rounds consist of a series of events, at monthly intervals, conducted at the AHSC. The inaugural event was a concert which initiated an art exhibit, MAGNUM OPUS. More than 120 works of students, faculty, and staff were exhibited in the AHSC library. The musicale which preceded the exhibit was performed by an ensemble, the Anna Magdalena Bach Quartet, whose members are spouses and friends of the faculty of the College of Medicine and a virtuoso performance by senior medical student Jonathan Hanks, who is also a master piano student. These two events were planned to coincide with the 20th Anniversary celebration of the College. In addition, the Pediatric Jazz Band, composed of pediatric faculty and friends, performed at a reception which followed the Founder's Day Program, another 20th Anniversary event.

The final program for 1987 was a roving chorale at Christmas performed by Arizona Repertory Singers, with English and American carols sung on the various patient units. Subsequent programs have been held monthly in 1988, at noon in the DuVal Auditorium, with a light, inexpensive lunch available in the foyer to provide a convivial atmosphere, and an enriching "break" in the workaday life of those at the AHSC. The first program featured William Wolfram, an internationally known artist, visiting the Tucson Symphony Orchestra, who gave an engaging piano performance with running explanatory commentary. One month later, a musical program was presented by first and second year medical students, their spouses and friends. The program consisted of a vocal chorale, a string quartet, a cello solo, and a piano duet and two solo piano performances. The third program of 1988 was a repeat performance by Jonathan Hanks, a master student under the tutelage of Ozan Marsh of the faculty of Fine Arts. These events have been festive and exceptionally well received by large, appreciative and attentive audiences. We have marveled at the hidden talents of our students, staff and faculty as these programs have evolved and the artists among us have been encouraged to perform.

This successful introduction of the performing arts into the Arizona Health Sciences Center environment has been a mutual goal which we have been able to achieve through the cooperation and efforts of performers, various divisions of the Center (the Arizona Health Sciences Center Library, the Division of Biomedical Communications, the Office of Medical Education, and the News and Communication Office) and the Dean's Office. Future plans include a slide/lecture entitled, Art and Illness, by a Phoenix psychiatrist, Thomas N. Thomas, M.D., featured recently in the AMA News. A steeldrum band, the Panhandlers, from the College of Music, will end the season for the academic year. We look forward to the continuation of the Dean's Cultural Rounds in the future. ❑

— Bertha Almagro
Assistant Director
AHSC Library
— Shirley Fulginiti
Co-Chairman
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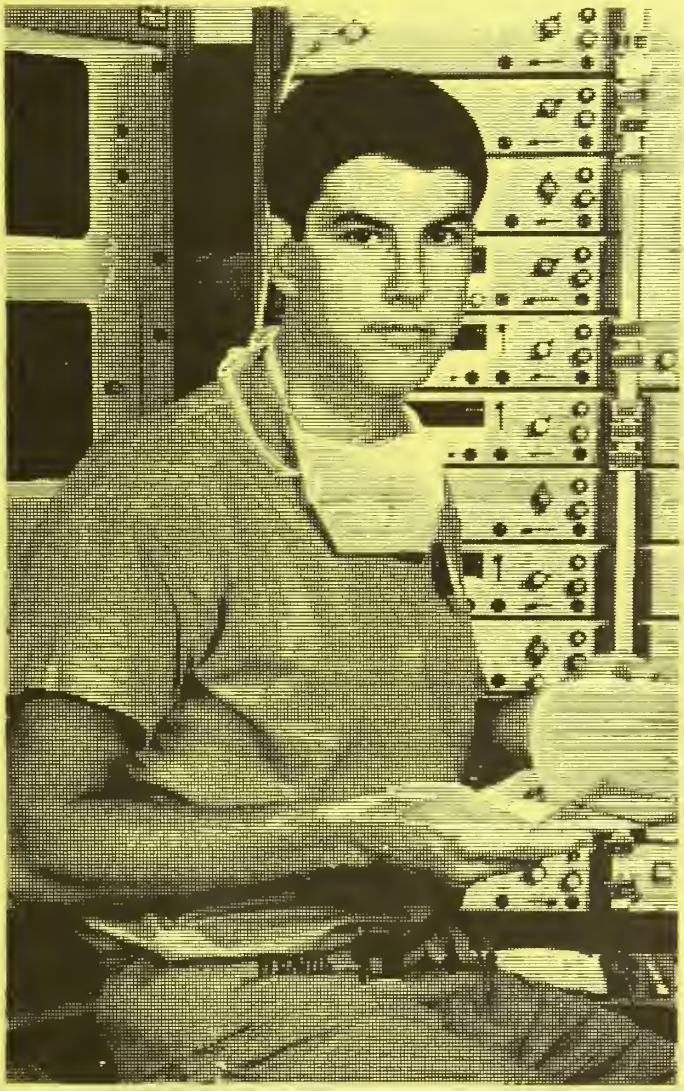

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Ann A. Caywood, M.D.
Family Practice
5143 W. Thunderbird Road, Glendale
University of Illinois College of Medicine, 1973

Todd P. Chapman, M.D.
Thoracic Surgery, Cardiovascular Surgery
13400 E. Shea Boulevard, Scottsdale
University of Missouri - Kansas City School of Medicine, 1980

Lise A. LaBarre, M.D.
Neurology
4550 N. 51st Avenue, Suite 27, Phoenix
University of Ottowa Faculty of Medicine, 1974

Bradley T. Lawrence, M.D.
Family Practice
2525 W. Greenway Road, Phoenix
University of Arizona College of Medicine, 1976

Robert F. Marschke, M.D.
Oncology, Hematology
13400 E. Shea Boulevard, Scottsdale
Baylor College of Medicine, 1975

Gregory K. Mayer, M.D.
General Surgery
1300 N. 12th Street, Suite 512, Phoenix
Tulane University School of Medicine, 1982

Jean C. Schuman, M.D.
Hematology, Oncology
13260 N. 94th Drive, Peoria
New York University School of Medicine, 1980

Franklin V. Tweedy, M.D.
Ophthalmology
9425 W. Bell Road, Sun City
University of Virginia School of Medicine, 1954

PIMA

David S. Shimm, M.D.
Radiation Oncology
Az Health Sciences Center, Dept. of Rad/Oncology 1925-B, Tucson
Duke University School of Medicine, 1977

NEW SERVICE MEMBERS

MARICOPA

Jay LeGrand, M.D.
Radiology, Nuclear Medicine
VA Medical Center, Phoenix
Faculty of Medicine & Surgery University of Bologna, 1968

Lloyd G. Pickering, M.D.
Family Practice, Aerospace Medicine
USAF Hospital, Williams AFB
University of Cincinnati College of Medicine, 1957

OUT OF STATE

Leslie R. Pedersen, M.D.
Psychiatry
2261 Sacramento Street, Suite 305, San Francisco
Rush Medical College - Chicago, 1984

NEW ASSOCIATE MEMBERS

COCONINO

David R. Hawkins, M.D.
Psychiatry
P.O. Box PP, Sedona
Medical College of Wisconsin - Milwaukee, 1953

Maricopa

Russell N. Brown, M.D.
Ophthalmology
222 W. Thomas Road, Phoenix
Ohio State university College of Medicine, 1941

Rolland Deputy, M.D.
General Practice, Emergency Medicine
40122 N. Vineyard Road, Queen Creek
Indiana University School of Medicine, 1941

George L. Garske, M.D.
Urology
1708 Staghorn Lane, Carefree
University of Minnesota Medical School - Minneapolis, 1944

NEW RESIDENT MEMBER

MARICOPA

David W. Kidwell, M.D.
Psychiatry
Maricopa Medical Center, Phoenix
Indiana University School of Medicine, 1983

Allan Reinfeld, M.D.
Internal Medicine, Cardiovascular Diseases
1111 E. McDowell Road, Phoenix
Institute of Medicine of Far Eastern University, 1982

Barbara J. Taylor, M.D.
Family Practice
6036 N. 19th Avenue, Suite 404, Phoenix
Oral Roberts University School of Medicine, 1986

PIMA

Daniel F. Walton, D.O.
Internal Medicine
3838 N. Campbell Avenue, Tucson
Philadelphia College of Osteopathic Medicine, 1984

(Continued on page 17)

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Physicians In The News

Paula L. Cho, M.D.

Paula Lee Cho, M.D., Ph.D., F.A.C.E.P., a Scottsdale Emergency Medicine specialist, has been elected president of the Arizona Chapter, American College of Emergency Physicians (ACEP) for 1988. Dr. Cho, a 1974 graduate of the University of Illinois College of Medicine, has been licensed to practice in Arizona since 1975.

Other 1988 Arizona Chapter ACEP officers are Thomas Patterson, M.D., President-Elect; Robert Nimlos, M.D., Secretary; and Peter Vann, M.D., F.A.C.E.P., treasurer.

Members of the 1988 Chapter Board of Directors are John Gallagher, III, M.D., F.A.C.E.P.; Marilyn Geninatti, M.D.; M. Ma. Guerrero, III, M.D., F.A.C.E.P.; Richard Horne, M.D., F.A.C.E.P.; Alan Kazan, M.D., F.A.C.E.P.; Michael Krentz, M.D., F.A.C.E.P.; John Lewis, M.D., F.A.C.E.P.; Steven Lipsky, M.D., F.A.C.E.P.; Harvey Meislin, M.D., F.A.C.E.P.; Fred Miller, M.D.; Arthur Sanders, M.D., F.A.C.E.P.; Gary Sollars, M.D., F.A.C.E.P.; and Louis Young, M.D.

Councillors for the Chapter for 1988 are Charles Goldstein, M.D., F.A.C.E.P.; Kenneth Iserson, M.D., F.A.C.E.P.; and John Raife, M.D., F.A.C.E.P.

Cardiac rehabilitation and fitness training specialist **Morton H. Dubnow, M.D.**, has been named team physician for the newly transplanted Phoenix Cardinals professional football team.

Dr. Dubnow, a board certified internist, said his new role won't stop his 20-year Phoenix medical career but will be an exciting and refreshing challenge. He will be on call all season to take care of the professional athletes whose futures' depend on their health and superb physical conditioning.

He will be required to attend all games, four during pre-season and 16 during the regular playing season, half of which are away games. Other responsibilities include evaluating college players prior to the annual draft and working with both coaches and trainers to establish training schedules.

A 1961 graduate of the University of Illinois College of Medicine, Dr. Dubnow was licensed to practice in Arizona in 1968 and has been an member of the Arizona Medical Association since 1969.

John C. Donaldson, M.D., was recently appointed chief of staff for Valley View Community Hospital, 12207 N. 113th Avenue, Youngtown. Donaldson, a staff member of Valley View since 1978, is a Fellow of the American College of Physicians and the American College of Chest Physicians. He also is a member of the American Medical Association and the Arizona Medical Society. Donaldson also is past president of the Western division of the Geriatrics Society.

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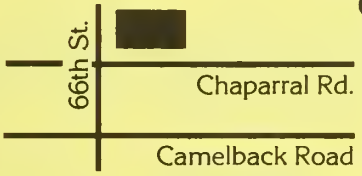

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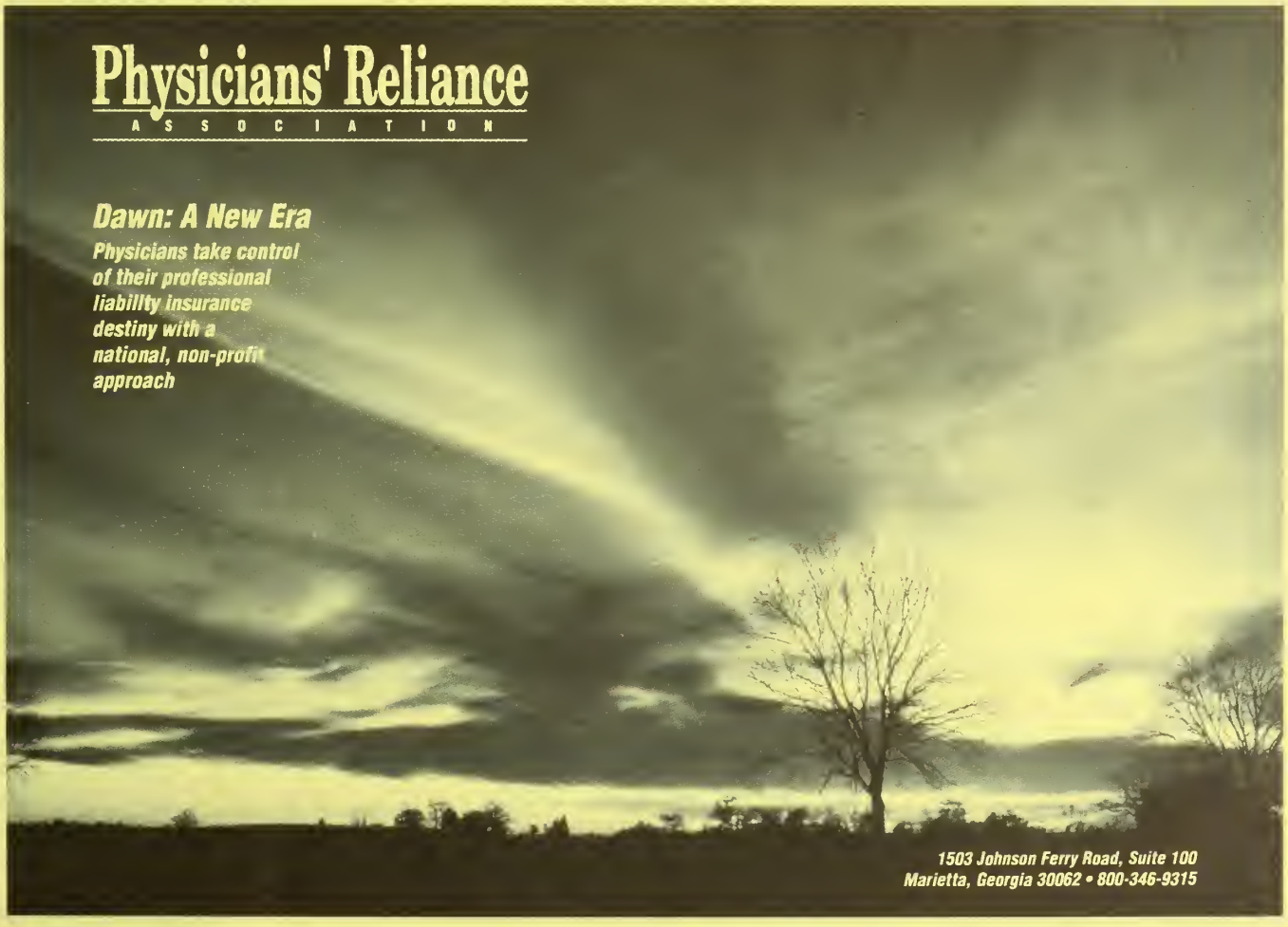

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by A.W. Middleton, Jr., M.D., President, Utah Medical Association

Guest Editorial

Congress has mandated a study on an alternative physician payment system by Drs. Hsiao and Braun at the Harvard University School of Public Health. Being developed for the past two years, it will establish a "resource based relative value scale (RBRVS)," which will establish relative values for thousands of procedures and will cover the services of eighteen separate specialties. The study is scheduled to be made public in July and has the potential of changing the entire fee schedule and payment system for every physician in the country. It is important, therefore, that all physicians understand the historical basis for the study. Then, once the study is made public, we will be prepared to evaluate it and react appropriately.

In 1979, Professors Hsiao and Stason published a resource based relative value study. That initial study was strictly theoretical and was never intended by the authors to be applied to the actual practice of medicine. They had decided that from an academic standpoint it would be useful to develop a RBRVS based on four "costs:" the time the physician takes to perform a service, the complexity of the service, the amortized opportunity costs of physician training, and overhead expenses. In developing that initial study, the professors wanted to show that the current, noncompetitive market for physician services resulted in an unjustified differential between prices charged by physicians for "cognitive" versus "procedural" services.

In 1983, the Massachusetts Rate Setting Commission (RSC) decided to apply this study to Medicaid physician reimbursement rates in Massachusetts. Despite the concerns of the Massachusetts Medical Society that the Hsiao study was theoretical and based on several arbitrary and challengeable assumptions, the RSC implemented the system.

Subsequently, under heavy pressure from the Massachusetts Medical Society and a number of other physicians, the RBRVS fee structure established for Massachusetts Medicaid payments was modified to restore the already inadequate rates for surgical services which had been further reduced under the system. Many physicians had simply refused to see Medicaid patients. The surgical fee reductions had to be rescinded so that access to surgical services might be restored to Massachusetts Medicaid patients.

The Massachusetts RSC then contracted with Professor Hsiao and Professor Peter Braun, M.D., to revise the RBRVS. That revision, completed in December of 1985, was produced using input from 110 physicians in eleven medical specialties. Upon close review by Massachusetts physicians, it was concluded that there were a number of assumptions made in developing that study which were "best guesses" on the part of Professor Hsiao, resulting in a final RBRVS which was "seriously flawed," according to the Massachusetts Medical Society.

All of the RBRVS studies by Professors Hsiao and Braun basically were developed by taking a "base procedure" for each specialty and then cross-indexing the relative value of that procedure to other specialties. They then used that cross-indexing to set relative values for every other procedure within the several compared specialties.

In the 1985 study, the Massachusetts Medical Society found that using different base procedures as the departure point resulted in significant differences in payment. For example, using appendectomy as the base procedure for general surgery, a rate of $233 would have been paid for an appendectomy in 1986. But if the base procedure was an inguinal hernia repair, the appendectomy rate would have been $274, a $41 difference.

The AMA became involved in 1984 when the House of Delegates adopted the Board of Trustees Report P which stated, "Payments for physicians' services often 'valued' cognitive services less highly than they did procedural services. To remedy potential problems in this area, the AMA Board believes it is necessary to address explicitly the relative values of physicians' services."

At the 1985 AMA annual meeting it was reported that HCFA had been

instructed by Congress to investigate RVS systems, and the AMA submitted a proposal in January of 1985 to "develop a new RVS based on the resource costs of providing physician services." That proposal, unfortunately, was rejected by the HCFA because the Federal Trade Commission raised antitrust concerns.

The AMA then initiated discussions with other groups who had submitted RVS proposals to HCFA. They eventually reached an agreement to participate with Professor Hsiao to develop an RBRVS for HCFA should the Harvard proposal be funded. One concern voiced by the Massachusetts Medical Society was that the AMA did not adequately address their concerns about the technical and methodology problems before forging an alliance with Professor Hsiao.

A national fee schedule seems the lesser of evils

As part of the AMA's agreement with Congress in lending its name to the Hsiao study, Congress agreed to hold off any further attempts to force mandatory assignment of Medicare payments, at least until the study was completed. Mandatory Medicare assignment had been one of Congress's high priorities before this joint venture with Professor Hsiao.

However, the RBRVS study has implications which could reach far beyond just Medicare. The results of this study could be applied across the board by any third-party payer to set physician payment rates. Many economists think our traditional charge based RVS system encourages high fees. Congress has the idea that the system is fueling the runaway costs of the Medicare Part B program. In evaluating the new RBRVS, we must compare it to some of the alternatives which Congress might impose, such as capitation or physician DRG's. When viewed in that light, a national RBRVS fee schedule seems the lesser of evils by a considerable margin.

Several specialties and subspecialities (mainly surgical) harbor grave doubts about this AMA/Harvard RBRVS. The major concern is that the entire system is significantly flawed in many of its assumptions. They question a number of the procedural methods used to derive the relative values. However, the AMA House of Delegates has consistently endorsed this study, while reserving the right to reject the results.

At the House of Delegates meeting in December of 1987, the delegates voted to give the Board of Trustees the responsibility to respond to this study when it is released next July and then to negotiate with HCFA on a plan for its implementation. One of the major AMA concerns about the entire study is that HCFA may try to combine the RBRVS with mandatory assignment for Medicare.

It is not a revolution

It will be interesting to note the response to this study at HCFA, where there remains a considerable amount of support for a capitation system. However, HFCA cannot ignore what essentially is a legislative mandate. Dr. Joseph Boyle, the Executive Vice President of the American Society of Internal Medicine (ASIM) and former AMA President, has stated that, "Congress wanted this study and has waited to tackle the issue of physician payment until the results are ready. Now it will look to HCFA to move toward a fee schedule based on RBRVS."

Professor Hsiao has stated publicly, "our study has already proved that cognitive services are inadequately reimbursed." From a practical standpoint the study will almost certainly give a bigger slice of the physician reimbursement pie to "cognitive" services such as history taking, physician examination, patient counseling and consultations as opposed to procedural services. Not surprisingly, the internists' family practitioners' and pediatricians' national organizations are among the study's biggest boosters. Procedurally oriented specialty associations have grave reservations about the study.

The Council of Medical Specialty Societies (CMSS) takes a mixed view of the study. Richard Wilbur, M.D., the Executive Director of the CMSS, states, "Many of us feel that it fails to take into account the individual physician's experience and skill. And it's not really sensitive to the complexity and severity of disease. That would be okay if all doctors had the same patient mix, but they don't. It is unfair to those who get the toughest cases."

However, Dr. Boyle of the ASIM states, "Cognitive services do appear to be getting relatively high ratings in the study, but not as high as some people hope. And procedural services aren't suffering as much as some people fear, either. It is not a revolution."

It appears that the best approach physicians can take toward this study is to simply be aware of its existence, be aware of its political and social ramifications, and be aware that it will be made public in July of this year. The AMA Board of Trustees has been mandated to scrutinize the study closely and has the power to reject it if it feels that portions of the study are significantly flawed. At this point we would do well as physicians to take a wait and see attitude. There will be ample opportunity for us to accept or reject the study, particularly when we compare it to the alternatives which government might have in mind for us.

We would do well to take a wait and see attitude

Here in Utah, in addition to restructuring the RVS system, we also must insist on a national system which will pay us fees that meet the average of fees paid to fellow physicians in other states for identical work. For years, Utah physicians have been paid rates which place us at the bottom of all states. The cost of living and the cost of providing medical care in Utah is not that dissimilar from most other states. As a matter of basic fairness, the physicians of Utah must be paid at rates brought up to the national average. In this regard, a national fee schedule may prove to be in our best interest. ❑

President's Page
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One significant limitation on peer support activities has been the committee's ability to confidentially discuss the specific facts of any individual's case. At present, any specific discussion or observations or evaluations done in support group are "discoverable" in court, which means any or all of the subcommittee members could be subpoenaed to testify.

If, however, confidentiality could be established, discussions between a defendant and the support group members could not be subpoenaed and used in court. That protection would allow the peer groups to look at the actual facts in the case and provide specific support and evaluation of the defendant's actual medical procedures.

The committee, with the help of its attorney, is investigating to find out if it is possible to devise a system to establish confidentiality.

Physicians seeking peer support should contact Misty Coumbe at the Arizona Medical Association's Phoenix headquarters office, 246-8901 in Phoenix, or toll-free, statewide, 1-800-482-3480.

—**Richard L. Collins, M.D.**

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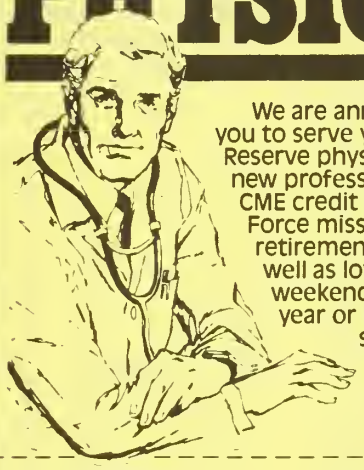

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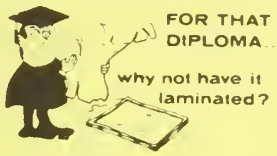

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Clinical Investigation

Prostacyclin Production Following In Vitro Mixing of Normal With Hemolytic-Uremic-Syndrome Serum

RICHARD L. SIEGLER, MD, *Salt Lake City;* JEAN B. SMITH, PhD, *West Lafayette, Indiana;*
MICHAEL B. LYNCH, MD, *and* SYED F. MOHAMMAD, PhD, *Salt Lake City*

Serum from patients with the hemolytic-uremic syndrome (HUS) usually has a diminished ability to support the production of prostacyclin (prostaglandin [PG] I_2). An impaired ability to produce this potent antiaggregatory substance could account for the thrombotic microangiopathy that is characteristic of the syndrome.

We did in vitro mixing experiments to determine if adding normal serum in various concentrations would improve the ability of HUS serum to support PGI_2 production when incubated with cultured human endothelial cells. Mixing normal with HUS serum in a 1:2, 1:3, and a 1:6 ratio generally enhanced the PGI_2-supporting capacity of the HUS serum. Moreover, adding normal serum yielded a mixture whose supporting capacity was between the normal and the HUS serum's value, and the PGI_2-supporting capacity could be predicted by calculating the weighted average value of the components of the mixture. There was a strong correlation between the calculated (predicted) and the actual experimental values ($r = .95, P < .001$).

(Siegler RL, Smith JB, Lynch MB, et al: Prostacyclin production following in vitro mixing of normal with hemolytic-uremic-syndrome serum. West J Med 1988 Jul; 149:37-39)

There is speculation that the hemolytic-uremic syndrome (HUS) results from a deficient production of prostacyclin (prostaglandin [PG] I_2) by vascular endothelial cells. A diminished ability to produce this potent platelet antiaggregatory substance in response to infectious or toxic vascular injury could account for the thrombotic microangiopathy that characterizes the syndrome. "Exhausted" rat[1-6] or human[7] aortic rings and cultured porcine[8] or human umbilical endothelial cells[9] generally display a diminished ability to produce PGI_2 when incubated with plasma or serum from children with the hemolytic-uremic syndrome. Moreover, there are reports of an improved or restored plasma PGI_2-stimulating capacity following plasma exchange or the intravenous administration of fresh frozen plasma (FFP).[1,7,10,11] These observations have led to the hypothesis that HUS plasma lacks a factor(s) necessary for the normal production of PGI_2 by endothelial cells and to the recommendation that FFP be used to treat the syndrome.

We have previously reported that serum from patients with the hemolytic-uremic syndrome generally has a diminished ability to support PGI_2 production by cultured human endothelial cells.[9] We have since carried out a number of mixing experiments to determine if adding normal serum in various concentrations could enhance the ability of HUS serum to support PGI_2 production.

Only patients with the classic features of the hemolytic-uremic syndrome—microangiopathic hemolytic anemia, thrombocytopenia, acute nephropathy—were included in the study; the project was approved by the Institutional Review Board, and informed consent was obtained from the parents.

Patients, Methods, and Materials

Our human endothelial cell model and PGI_2 determination methods have previously been described in detail.[9] Briefly, endothelial cells were harvested from human umbilical veins, suspended in a mixture of 80% medium 199 (M199, MA Bioproducts) and 20% human serum, and added to tissue culture plate wells. They were fed periodically with a mixture of M199 and human serum until a confluent monolayer of cells was obtained.

The patients' serum specimens were drawn during the first week of the syndrome and before any blood or blood products had been given. Because an individual patient's serum specimen volumes were often insufficient for all three mixtures—that is, 1:2, 1:3, 1:6—a total of 34 mixing experiments were done on serum specimens taken from 20 patients. All but one of the patients had the classic postdiarrheal hemolytic-uremic syndrome. One child had a nondiarrheal idiopathic form of the syndrome. No familial or relapsing cases of the hemolytic-uremic syndrome were studied.

The experiments were done by first washing the cells with a phosphate-buffered saline solution to remove any media or PGI_2. Then 1 ml of an individual solution containing either 20% unmixed patient serum and 80% M199 or 20% of a 1:2, 1:3, or 1:6 mixture of normal to individual HUS serum and 80% M199 was added to cells in each of three wells.

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ABBREVIATIONS USED IN TEXT

FFP = fresh frozen plasma
HUS = hemolytic-uremic syndrome
PG = prostaglandin
PGI_2 = prostacyclin
SD = standard deviation

The cells were incubated at 37°C, specimens were taken at zero and six hours, indomethacin was added to stop further PGI_2 production, and the specimens were frozen. PGI_2 production was determined by radioimmunoassay of its stable metabolite, 6-keto-$PGF_{1\alpha}$. Producing PGI_2 (6-keto-$PGF_{1\alpha}$) by this model depends both on the source of the serum and the source of endothelial cells. To permit valid comparisons of 6-keto-$PGF_{1\alpha}$ production by endothelial cells from different umbilical veins, 6-keto-$PGF_{1\alpha}$ production in the presence of the same normal serum was determined for each source of endothelial cells. This normal serum (control) was assigned a value of 1.00, and all reported 6-keto-$PGF_{1\alpha}$ values are expressed in relationship to the control value. For example, a value of 0.75 indicates that the serum supports production of 75% as much 6-keto-$PGF_{1\alpha}$ as the control serum for that source of endothelial cells. The control serum was also used as the "normal serum" in the mixing experiments.

Intra-assay and interassay variation for the radioimmunoassay was 5.2% and 11.9%, respectively. Reported values represent the mean for the three wells. The average coefficient of variation for five subjects was 8.3%.

Baseline (before mixing) values were compared with a value of 0.87 ± 0.18 obtained from 22 healthy children.

The weighted average (calculated value) was determined using the following equation for a mixture of normal serum: HUS serum with a ratio of 1:N, when N indicates the dilution ratio:

$$\frac{\text{normal value} + (\text{HUS value})\ N}{1 + N}$$

All values are expressed as the mean ± the standard deviation (SD), and the statistical significance of differences in 6-keto-$PGF_{1\alpha}$ concentrations, before and after adding normal serum, was analyzed using the Wilcoxon signed rank test for nonparametric paired data.

Results

Adding normal to HUS serum had little effect on PGI_2—that is, 6-keto-$PGF_{1\alpha}$—production in the seven patients (six with postdiarrheal hemolytic-uremic syndrome, one with a nondiarrheal, idiopathic form) whose baseline (unmixed) values were already above the mean of 0.87 as determined for 22 healthy children.

In the 13 patients—all had the classic postdiarrheal syndrome—whose baseline values were below 0.87, however, adding normal serum yielded a mixture whose PGI_2-supporting capacity was between the normal and the HUS serum's value and was in general proportional to the weighted average value of the components of the mixture. The calculated (predicted) values for all specimens—those with baseline values both above and below the normal mean for healthy children—correlated strongly ($r = .95$, $P < .001$) with the actual experimental values (Figure 1).

Moreover, mixing normal with HUS serum having baseline values below the mean for healthy subjects, in a 1:2 (five patients), 1:3 (eight patients), and a 1:6 (seven patients) ratio resulted in increases from 0.46 ± 0.22 to 0.74 ± 0.27 ($P = .02$), 0.58 ± 0.26 to 0.68 ± 0.19 ($P = .08$), and 0.63 ± 0.23 to 0.70 ± 0.17 ($P = .11$), respectively (Figure 2). The PGI_2-supporting capacity increased in all five of the 1:2 mixtures, in five of the eight 1:3 mixtures, and in five of the seven 1:6 mixtures. All but 3 (one in each of the mixing ratio subsets) of the 20 mixtures acquired an ability to support PGI_2 production that was within 2 SD of the mean for healthy children. The three mixtures that remained more than 2 SD below the mean for healthy children—that is, < 0.51—had three of the lowest baseline values and did increase substantially (0.29 to 0.44, 0.19 to 0.38, and 0.20 to 0.41) with mixing.

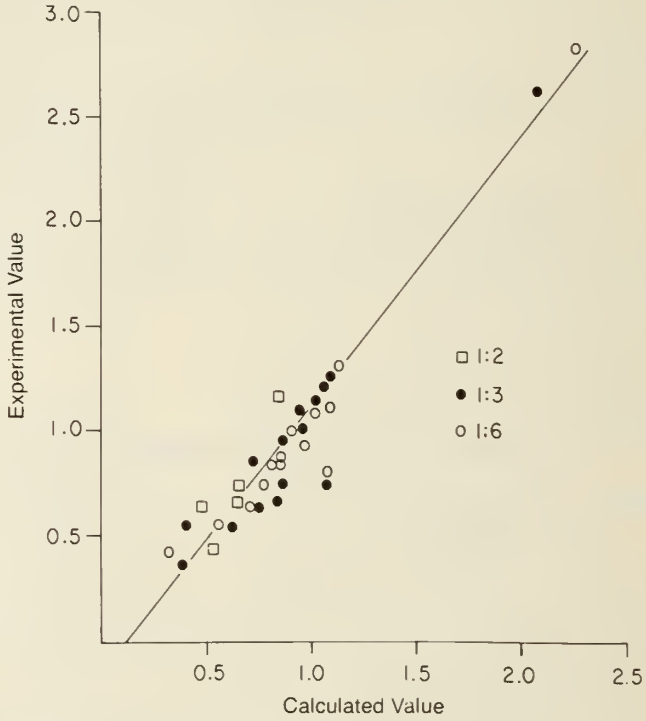

Figure 1.—The graph shows a comparison of experimental and calculated (predicted) values assuming a weighted average value for mixing normal serum with serum from children with the hemolytic-uremic syndrome. Patients with baseline values both above and below the mean of 0.87 determined for healthy children are included. $y = 1.21x - 0.14$; $r = .95$, $P < .001$; $n = 34$

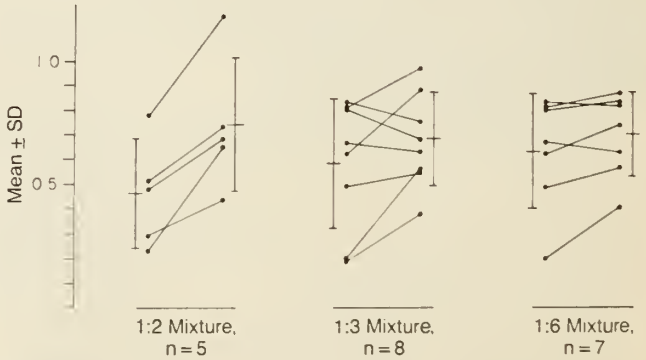

Figure 2.—The graphs show the prostacyclin-supporting capacity before and after mixing normal serum with serum from children with the hemolytic-uremic syndrome whose baseline values were below the mean of 0.87 determined for healthy children. SD = standard deviation

Discussion

While there are reports of improved or restored PGI_2-stimulating capacity, as measured by bioassay (such as using "exhausted" human or rat aorta) after administering FFP to small numbers of patients with the hemolytic-uremic syndrome,[1,7,10] there are no reports of in vitro mixing experiments.

We had reasoned that because of the small sample size and nonrandomization of the clinical reports, we first wanted to test the "missing factor" hypothesis ex vivo before subjecting our patients to the risks and expense of FFP therapy.

Our observations do support the hypothesis that HUS serum (or plasma) is deficient in a factor or factors needed to stimulate (or support) PGI_2 production by endothelial cells, and they corroborate the in vivo experience that intravenously administering FFP to patients with the syndrome can improve the PGI_2-stimulating capacity.[1,7,10] It is not clear, however, whether the PGI_2-stimulating defect precedes the onset of the hemolytic-uremic syndrome or results from it. It may be that the HUS plasma and serum have a decreased ability to stimulate or support PGI_2 production in the ex vivo models—such as rat aorta or cultured endothelial cells —because a "stimulatory" factor or factors have previously been consumed or exhausted by endothelial injury and subsequent PGI_2 production. Moreover, in a recent prospective controlled trial of FFP therapy, Rizzoni and co-workers were unable to show a favorable effect on the clinical outcome.[12] Even so, based on the strong correlation we found between the calculated (predicted) value and the actual experimental value (Figure 1), we speculate that any improvement in PGI_2-supporting capacity following plasma infusions or exchange would be directly related to the difference between the patient and replacement serum values and to the volume of infusion or exchange.

It is tempting to extrapolate our in vitro experience to the clinical situation. An infant, for example, with a hematocrit of 25% would require about 30 ml of FFP per kg of body weight to achieve the degree of response we observed with our 1:2 (normal serum:HUS) serum mixture. This, in fact, is the loading volume of FFP currently recommended for the treatment of the syndrome.[13] Moreover, the results we noted following our 1:3 mixture would require about 20 ml per kg of FFP, which is also the currently recommended daily maintenance dose of FFP.[13] It must be remembered, however, that these volumes of FFP are substantial and can produce severe fluid overload and hypertension in an oliguric child. Frequent or continuous ultrafiltration is therefore generally required when administering FFP volumes of this magnitude to patients with the hemolytic-uremic syndrome who have oliguria.

In summary, our data show that the PGI_2-supporting capacity of HUS serum is generally low and improves following the in vitro addition of normal serum. Our study does not, however, resolve the uncertainty regarding the role of PGI_2 production in the pathogenesis of the hemolytic-uremic syndrome or the advisability of administering FFP to such patients.

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Delta Hepatitis in Denver

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The prevalence of hepatitis D virus (HDV) infection in patients with hepatitis B virus (HBV) infection in the mid-United States is not well defined. We tested 65 patients seen between 1983 and 1986 with HBV infection in Denver for evidence of coexisting HDV infection. Five patients had anti-delta (δ) antibody. The prevalence of HDV infection was higher in patients with chronic hepatitis B (4/37) than in patients with acute hepatitis B (1/28). The prevalence of HDV infection in male homosexuals (3/32) was similar to reported figures, but the incidence of δ-infection in intravenous drug users in Denver was unusually low (1/16). In comparison to Los Angeles, New York, southern Italy, and Sweden, Denver appears to have a low incidence of HDV infection, which probably reflects its low prevalence in the drug-using population.

(Rector WG Jr, Govindarajan S, Penley KA, et al: Delta hepatitis in Denver. West J Med 1988 Jul; 149:40-42)

Ten years ago a new hepatitis virus, the delta (δ) agent, was described.[1] The δ-agent, now known as hepatitis D virus (HDV), is a small, defective ribonucleic acid virus that depends on the hepatitis B virus (HBV) for its own replication. The broad outlines of the epidemiology of HDV infection have been drawn, but significant gaps remain. In particular, there is little information about the prevalence of HDV infection in the mid-United States. We report the incidence and epidemiologic pattern of infection with the δ-agent in Denver, Colorado.

Patients and Methods

There were two sources of patients in this study. The first was 43 patients with hepatitis B infection seen in the Hepatitis Clinic of Denver General Hospital from about November 1985 to November 1986. The second was 22 homosexual men with chronic hepatitis B infection followed by the Disease Control Service at Denver General Hospital. These patients had participated in hepatitis B prevalence and incidence studies[2] and in a hepatitis B vaccine trial.[3] Stored serum (−70°C) obtained between 1982 and 1986 was available on these patients.

Hepatitis B surface antigen (HBsAg) and immunoglobulin (Ig) M antibody to hepatitis B core antigen (anti-HBc) were measured by commercially available radioimmunoassays (Ausria II and Corab, respectively, Abbott Laboratories). IgG and IgM antibodies to the δ-agent were measured by solid-phase-capture radioimmunoassay.[4,5]

Acute hepatitis B was diagnosed on the basis of a typical clinical picture with a pronounced increase in serum aminotransferase levels and evidence of anti-HBc IgM. All but one of the 28 patients with acute hepatitis B also had HBsAg. Chronic hepatitis was diagnosed as type B on the basis of the presence of HBsAg. Acute HDV infection was diagnosed on the basis of a low titer or the absence of IgG antibody to the δ-agent and the presence of a high titer of IgM antibody to hepatitis D. Chronic HDV infection was diagnosed on the basis of a high titer of IgG antibody with a low titer of IgM antibody to the δ-agent.

Results

Of 65 patients with HBV infection, 5 had HDV superinfection (Table 1). The probable sources of hepatitis B and δ-infections were intravenous drug use (one patient), male homosexual activity (three patients), and inapparent (one patient). There were no overlapping risk factors. The intravenous drug user had acute hepatitis B and acute HDV infection. The other four patients had chronic hepatitis B and superimposed δ-infection. In two of these patients, both male homosexuals, HDV infection presented as acute hepatitis. Chronic HDV infection developed in one, resulting in chronic active hepatitis that progressed to biopsy-proved cirrhosis within two years. The other patient did not return for follow-up after his acute hepatitis subsided. The other two patients with chronic hepatitis B presented with coexisting chronic HDV infection. One was asymptomatic and had a serum aspartate aminotransferase concentration of less than twice normal. She refused liver biopsy. The second patient was mildly fatigued and had a serum aspartate aminotransferase concentration five times normal. He discontinued visits before further evaluation could be done.

Discussion

Hepatitis D virus is newly described.[1,6] It is unique in being dependent on the HBV for its own replication and survival.[6] Consequently, HDV infection only occurs in patients with coexisting HBV infection. This dual infection may take the form of acute HDV plus acute HBV infection, acute HDV infection superimposed on chronic HBV infection, or concurrent chronic HDV and chronic HBV infections. The addition of HDV infection to HBV infection increases the severity of hepatic inflammation.[6] Patients with acute δ-infection superimposed on HBV infection (either acute or chronic) frequently go on to have fulminant hepatic

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ABBREVIATIONS USED IN TEXT

anti-HBc = antibody to hepatitis B core antigen
HBsAg = hepatitis B surface antigen
HBV = hepatitis B virus
HDV = hepatitis D virus
Ig = immunoglobulin

failure.[4,6,7] Patients with chronic HBV and δ-agent infections usually have chronic active hepatitis progressing to cirrhosis.[6-9]

A general outline of the worldwide epidemiology of HDV infection has taken shape in the decade since the first description of the δ-antigen and antibody system (Table 2). HDV infection complicates hepatitis B virus infection with a relatively high frequency in Italy and Scandinavia. A high incidence of HDV infection has been described among Indians in Venezuela and natives of Northwest Kenya. Infection with the δ-agent is relatively infrequent throughout Asia and in Australia.

In the United States, surveillance of patients with hepatitis B infection for HDV superinfection has mainly been done in large urban centers on the East and West coasts (Table 2). These areas, in particular California and New York, have had relatively high incidences of HDV infection. In surveys of HBsAg-positive blood donors throughout the United States, δ-antibodies were found in 4% of subjects.[10] The highest frequency (12%) was in San Jose, California, and the lowest in the south-central states (1%). These figures probably somewhat underestimate the frequency of δ-infection in this country. HDV infection usually produces severe hepatocellular injury, and acceptable volunteer blood donors have no history of liver disease. The present report, however, documents only a slightly higher incidence of HDV infection

TABLE 1.—*Prevalence of Hepatitis D Virus Infection in Denver, 1982-1986*

Patient Source	*Hepatitis Clinic*		*Disease Control Service*
Period of surveillance	1985-1986		1982-1986
Type of infection	Acute	Chronic	Chronic
Source of infection*			
Male homosexual	0/4	1/6	2/22
Intravenous drug use	1/12	0/4	0
No obvious source	0/10	1/4	0
Miscellaneous†	0/2	0/1	0
Totals	1/28	2/15	2/22

*The numbers indicate persons with the δ-agent/patients with hepatitis B.
†Transfusion (1) and birth in an endemic area (Vietnam, 1).

TABLE 2.—*Epidemiology of δ-Infection*

Location	*Source*	*Period of Surveillance*	*Acute HBV Infection**	*Chronic HBV Infection**
Italy	Rizzetto et al, 1979[9]	NS	...	48/227
	Raimondo et al, 1982[11]	1979-1981	63/98†	41/63†
	Smedile et al, 1983[12]	1978-1981	99/687	238/1,314
	Arico et al, 1985[13]	1981-1984	...	112/2,487‡
	Maggiore et al, 1985[14]	1974-1982	...	13/102§
France	Rizzetto et al, 1980[15]	NS	...	1/92
Germany	Rizzetto et al, 1980[15]	NS	...	3/153
Poland	Rizzetto et al, 1980[15]	NS	...	1/50
Switzerland	Raimondo et al, 1982[11]	1974-1981	6/17†	5/16†
Greece	Tassopoulos et al, 1986[16]	NS	...	4/167
Scandinavia	Rizzetto et al, 1980[15]	NS	...	9/19
	Hansson et al, 1982[17]	1970-1981	...	41/57
	Raimondo et al, 1982[11]	1974-1981	3/7†	5/11‡
	Lindh et al, 1986[18]	NS	...	15/60
	Hess et al, 1986[19]	NS	...	2/44‖
Ireland	Raimondo et al, 1982[11]	1974-1981	15/49†	...
Great Britain	Weller et al, 1983[20]	NS	...	9/71
Taiwan	Rizzetto et al, 1980[15]	NS	...	4/53
Japan	Rizzetto et al, 1979[10]	NS	...	2/86
	Rizzetto et al, 1980[15]	NS	...	2/152
Australia	Rizzetto et al, 1980[15]	NS	...	1/21
Kenya	Thomas, 1985[21]	NS	...	NS (65%)
Venezuela	Hadler et al, 1984[22]	1981-1982	...	47/83
USA, NJ	Rizzetto et al, 1979[10]	NS	...	8/25
NJ	Rizzetto et al, 1980[15]	NS	...	8/35
NY	Rizzetto et al, 1979[10]	NS	...	5/24
Mass	Jacobsen et al, 1985[23]	1976-1984	6/114	15/110
Md	Rizzetto et al, 1980[15]	NS	...	0/81
Calif	Rizzetto et al, 1980[15]	NS	...	13/40
Calif	De Cock et al, 1986[24,25]	1967-1985	17/358	45/200
Minn	Shiels et al, 1985[26]	1969-1983	1/68	28/464
Colo	Present report	1983-1986	1/28	4/37

HBV=hepatitis B virus, NS=not stated

*The number with infection with the δ-agent versus the number with HBV infection.
†Intravenous drug users.
‡Asymptomatic carriers.
§Children.
‖Male homosexuals.

in patients with clinically evident hepatitis B in Denver (5/65, 8%).

Antibodies to HDV frequently rise late in the course of acute HDV infection.[6] Arguably, our estimate of the frequency of HDV coinfection in patients with acute hepatitis B could be falsely low. Such patients were typically seen first in primary care facilities, however, and had reached the peak of their illness or were in the convalescent phase when a serum specimen was drawn in the Hepatitis Clinic for HDV antibodies. Consequently, the number of false-negative diagnoses was probably minimal.

HDV infection appears to be transmitted most efficiently by the parenteral route.[6] Most centers have reported the highest incidences in persons with hemophilia and in intravenous drug users.[9,11,12,15,17,20] The HDV is infrequently transmitted by male homosexual activity. We found a 10% incidence of HDV infection in homosexual men with HBV infection. This is comparable to other reported figures.[19,24] In contrast, the incidence of HDV infection in intravenous drug users in Denver (1/16) is considerably lower than that cited in most other reports.[9,11,12,15,17,20] HDV coinfection rates in this group have been rising steadily in Sweden.[17] The relative infrequency of HDV infection in Denver at present may indicate only that we are in the early stages of a developing epidemic. Continued surveillance will be necessary to define secular trends.

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Malignant Melanoma—Profile of an Epidemic

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Cutaneous malignant melanoma is occurring in epidemic proportions in the United States. To provide a profile of persons at risk and the epidemiologic features of malignant melanoma, we reviewed the records of 325 patients with cutaneous malignant melanoma seen at the University of Colorado Health Sciences Center between 1973 and 1983. Most patients had fair skin, brown or blonde hair, blue or green eyes, and had difficulty in suntanning. The majority of melanomas (72%) developed in preexisting nevi. In women, melanomas were most common on the extremities, and in men they occurred most frequently on the trunk, head, or neck. The most frequently noted depth of invasion was Clark's level IV. At diagnosis, most of the patients (77%) were at stage I. We conclude that malignant melanoma constitutes a major disease problem in the western United States that is largely preventable with appropriate physician and patient education.

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Cutaneous malignant melanoma is one of the most rapidly increasing malignant lesions in the United States, particularly in the western region. Over the past 50 years, there has been a 600% increase in the incidence of the disease in the United States.[1] In the past ten years, the age-adjusted incidence in the Denver area has increased from 6.0 to 11.4 per 100,000 population among white men and from 6.0 to 9.7 per 100,000 among white women (Colorado State Department of Health, oral communication, July 1985). Similar experiences have been reported from other western states.[2,3]

There is little doubt that this dramatic rise in the incidence of malignant melanoma is the result of increasing exposure to ultraviolet light in the form of sunshine.[4-10] Evidence supporting this will not be discussed in detail here but may be found in the references noted. It is important to realize that the high incidence in the western United States is probably the result of increased levels of ultraviolet radiation from abundant sunshine coupled with changes in clothing habits and alterations in life-styles that have led to considerable increases in time spent out of doors. This is vital because it suggests that cutaneous malignant melanoma may be in large part a preventable disease.

With the current epidemic, patients with malignant melanoma are likely to be seen by physicians of many specialties. All need to be familiar with the clinical features of the disease, recognizing the patients at high risk, and the best means of treatment. Early diagnosis and surgical excision are the most important factors in cure.

In response to a rapidly increasing patient load, a clinic dedicated exclusively to malignant melanoma was established at the Clinical Research Center of the University of Colorado Health Sciences Center, Denver, in 1973. Since then we have seen 325 patients with malignant melanoma. Reported here are the clinical characteristics of these patients and the features of the disease as seen at our institution from 1973 to 1983. Recommendations for prevention and early diagnosis are made for physicians likely to see such patients in their practice. Our hope is that this report will serve to focus more attention on the problem of malignant melanoma, particularly in the western United States.

Patients and Methods

We reviewed the records of all patients seen between 1973 and 1983 at the University of Colorado Health Sciences Center with a diagnosis of malignant melanoma. Most of these patients were examined and followed by the authors in the Malignant Melanoma Clinic of the Clinical Research Center. Data for each patient were recorded in a uniform fashion and then entered into a computer-based data registry for compilation and analysis. Not all data were available on each of the 325 patients; therefore, percentages have been recorded as the proportion of patients for whom this information was available. When possible, patients or family members or both were questioned directly and patients examined to ensure accuracy of the data collected. In addition to clinical data, phenotypic characteristics of the patients—eye color, hair color, skin pigmentation, and so forth—were recorded.

For determining the depth of invasion of cutaneous melanomas, we used Clark's method.[11] More recently, we have begun to include a measurement of the depth of invasion in millimeters as described by Breslow.[12] This information was not available on most patients, so we report here only Clark's levels.

A three-tiered staging technique was used. In stage I, the melanoma is confined to an initial primary site or there are satellite lesions within 5 cm of the primary. Stage II includes melanoma with in-transit metastases between the primary and the lymph node drainage, but more than 5 cm away from the original lesion, or with regional lymph node metastases.

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Stage III melanomas are those that have spread beyond the regional lymph node drainage.

Results

For the ten-year period studied, complete or partial data were available on 325 patients. Table 1 shows the age and sex of all patients at the time of diagnosis: 147 women and 178 men for a female-to-male ratio of 0.82:1. The youngest patient seen was 14 years and the oldest patient was 81 years.

Partial phenotypic data were recorded on 220 of the 325 patients and are given in Tables 2 through 4. Of the 208 patients in whom hair color was recorded, only 12 (6%) had black hair (Table 2). The most common hair color recorded, by either the patient or the observer, was brown (52%). It should be noted that it was uncommon for patients with malignant melanoma to have red hair (13%). There is a common misconception that persons with bright red hair and freckles are those in whom malignant melanoma is most likely to develop. As can be seen, this was not borne out by our data. The percentage of whites in the Colorado population with various hair color has not been determined in a controlled group. Whether the findings noted here differ from those of a control white population has not been determined. Of the 179 patients in whom eye color was recorded (Table 3), most had blue eyes (44%). All of the other patients had either brown eyes (31%) or some variation of green eyes (26%). Skin color was recorded in 207 patients (Table 4). Of the 325 patients, 74% regarded themselves as pale or fair. The majority indicated that they had difficulty suntanning. Only three patients reviewed were black, and only two others were dark complected.

The morphologic types of cutaneous melanoma were identified in 213 patients. Superficial spreading melanoma was the most common type, occurring in 71% of the total. This is similar to the percentage reported in other series.[13] Nodular melanoma, which is less commonly associated with ultraviolet exposure, accounted for 23% of patients. Lentigo maligna, which occurs on the face primarily in elderly populations, accounted for only 6% of the cases.

The most common presenting symptom of a malignant melanoma was an increase in size of a nevus followed by color change. Bleeding, elevation, itching, oozing, and pain were less common and tended to indicate a more advanced lesion.

The location of the primary lesion was recorded and compared in men and women. In male patients, the most common site was the trunk (51%). The upper and lower extremities account for only slightly more than 20% of presenting lesions. In contrast, the extremities accounted for the site of melanoma in slightly more than 50% of women. The lower extremities were the most common site, accounting for 30%. These findings are similar to those reported by previous authors.[14-16]

Table 5 shows the level of invasion of melanomas in 232 patients. The level of invasion most frequently seen was Clark's level IV, which accounted for 109 of the 232 (47%) patients in whom this information was recorded. Thin melanomas (levels I and II) were uncommon in our series, representing only 19% of primary lesions. Levels III, IV, and V patients accounted for 81% of the total. This is noteworthy because these patients have a high likelihood of recurrence from occult micrometastases that cannot be eradicated by any current means of therapy. Further, these data indicate that these lesions were diagnosed and excised relatively late.

TABLE 1.—*Age at Diagnosis of Patients With Cutaneous Malignant Melanoma, N=325*

	Men	Women	Combined
Number (%)	147.0 (45)	178.0 (55)	325.0
Mean age at diagnosis (range), yr	41.3 (19-81)	41.5 (14-78)	41.4
Median age at diagnosis, yr	39.0	38.0	38.5

TABLE 2.—*Hair Color in Patients With Cutaneous Malignant Melanoma, N=208*

	Patients	
Hair Color	Number	Percent
Brown	108	52
Blonde	54	26
Red	26	13
Black	12	6
Auburn	8	4

TABLE 3.—*Eye Color in Patients With Cutaneous Malignant Melanoma, N=179*

	Patients	
Eye Color	Number	Percent
Blue	78	44
Brown	55	31
Hazel	24	13
Green	22	12

TABLE 4.—*Skin Color in Patients With Cutaneous Malignant Melanoma, N=207*

	Patients	
Skin Color	Number	Percent
Pale/fair	154	74
Medium	48	23
Black	3	1
Dark	2	1

TABLE 5.—*Clark's Level of Invasion of Cutaneous Malignant Melanoma, N=232*

		Patients	
Level	Clinical Depth of Invasion	Number	Percent
I	Dermal-epidermal junction	2	1
II	Papillary dermis	41	18
III	Upper reticular dermis	70	30
IV	Lower reticular dermis	109	47
V	Subdermal layers	10	4

TABLE 6.—*Stage at Diagnosis of Patients With Cutaneous Malignant Melanoma, N=325*

	Patients	
Stage	Number	Percent
I	250	77
II	49	15
III	26	8

Our findings are similar to those reported by some authors[14,17] but in opposition to the findings of others who noted that thin melanomas are now more commonly seen.[18] Table 6 shows the stage at diagnosis of our patient population. Only a few patients presented with metastatic disease. Most were classified as stage I (77%) or stage II (15%).

A total of 262 patients were questioned as to whether their melanoma began in a preexisting nevus. Most (52%) indicated that the melanoma did not arise de novo but instead began in a mole that had been present for ten years or longer. Others (20%) felt the melanoma had begun in a nevus present for less than ten years. Only 28% of the patients felt that the melanoma has arisen as a new lesion. This is similar to previous data in which it has been suggested that most melanomas arise in preexisting nevi.[1] In the present study, this information was not confirmed by histopathologic criteria that would indicate that the melanomas arose in preexisting nevi, and thus the subjective reporting may have been higher than actually occurs.

Discussion

There is little doubt that we are faced with an epidemic of malignant melanoma, especially in the western United States. The rise in incidence of this highly malignant and often fatal neoplasm has been well documented by a number of investigators over the past 10 to 20 years.[2,3,5,6,19]

Most investigators, including ourselves, believe that the cause of this alarming trend is increasing exposure to ultraviolet light in the form of sunshine. New clothing habits and changes in life-style appear to be prime contributors. The bulk of evidence, including population migration studies, correlation of the incidence of the disease with ultraviolet light levels, phenotypic studies of persons likely to acquire malignant melanoma, and differences in the sites of melanoma in men and in women, would seem to support this contention.[4-10] As to the last, our studies indicate that back, head, and neck melanomas are more likely in men, while extremity melanomas occur more frequently in women. This has been attributed to differences in clothing habits. It will be interesting to see if these patterns continue as further changes in clothing style evolve.

In the past, numerous additional etiologic factors have been mentioned. These include sunspot activity[20] and exposure to fluorescent lights.[21] We, however, find the ultraviolet light data incontrovertible and think there should be a major campaign to make physicians and the public aware of the dangers of excessive exposure to sunshine.

Despite the strong correlations between exposure to ultraviolet light, skin color, and the development of malignant melanoma, we have found that not all cutaneous malignant melanomas develop in sun-exposed sites. Thus, it would appear that the role of ultraviolet light is not entirely the result of direct exposure of melanocytes to the sun itself. Rather, available evidence suggests that there may be a circulating factor involved in the development of malignant melanoma.[22] We have suggested and are currently investigating the possibility that this may be melanocyte-stimulating hormone.

Finally, we have shown in the present study that most cutaneous malignant melanomas in Colorado are diagnosed when the primary lesion is at level IV. This carries a subsequent 30% to 40% chance of recurrence despite adequate resection of the primary lesion.[11,23,24] This suggests that most lesions are being diagnosed and removed at a considerably later time than is desirable to obtain long-term and permanent cure. Thus there is tremendous need for an intense educational program for physicians and the general public.

One of the most distressing findings not detailed in the present report is that 15% to 20% of our patients indicated they had shown the malignant lesion to a physician a year or two before it was actually removed, only to be told not to worry about it. As a result, current teaching recommends removing any pigmented or suspicious lesion about which a patient complains or about which the physician is concerned. This should be done without hesitation with the exception of those lesions that are in cosmetically difficult areas. For these patients, referral to a plastic surgeon or a dermatologist would seem appropriate. Large, cosmetically difficult pigmented lesions can be evaluated by a punch or incisional biopsy, but for all other lesions, total excision is more appropriate.

Due to the epidemic proportions of this disease, every practicing physician, particularly those in the western United States, needs to be familiar with malignant melanoma. The most important clinical signs and symptoms for both patients and physicians are any change in a preexisting mole but particularly an increase in size, a change in color, or the development of an irregular, notched border. The change in color may include increasing areas of darker or lighter pigmentation. The classic malignant melanoma has a variegated color, with areas that are brown and other areas that are pink, white, or black. The development of a new mole, particularly when associated with itching or bleeding or both, is also an important clinical finding. It is also essential that physicians counsel their patients about the dangers of ultraviolet exposure, be able to recognize persons who are at high risk for the development of the disease, recognize potentially malignant lesions, and remove them early. Based on our own investigations over the past ten years, we make the following recommendations:

- The public should be educated about the dangers of ultraviolet exposure and the potential development of malignant melanoma.
- Physicians should recognize persons who are at high risk for the development of malignant melanoma. These are people who are fair-skinned, unable to suntan, usually have light brown or blonde hair and blue eyes, and who frequently have several nevi.
- All persons, but particularly those who are phenotypically susceptible to malignant melanoma, should be advised to wear protective clothing and sunscreens. Sunbathing should be avoided, and moles about which patients are concerned should be promptly evaluated.
- Physicians should remove, without hesitation, any pigmented lesion about which patients or physicians are concerned.

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AIDS

THE ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS) is going to affect us in many ways that were not immediately apparent. Something that is becoming very obvious in almost all hospitals is that there's an extreme nursing shortage. Nursing schools are closing. Nursing registration is down by 24%, and graduates are not going into bedside nursing. The vacancy rate for nurses in many hospitals, nationally, is 13%, whereas several years ago it was 6%.

Patients with AIDS are persons who did not previously require any medical care. This is a new disease in the population, and the issue of finding the health providers, both doctors and nurses, to care for these persons is going to be a very real one that has to be faced over this evolving period of time.

The key issue in my mind is prevention of AIDS. We are not going to have a vaccine in the foreseeable future, and when we do, it won't affect those people who are now infected. Prevention rests in dealing with: needles and intravenous drug use; the administration of blood products through blood banks; changing sexual habits for those who have already established their sexual habits; and doing everything we can to ensure that the sexual habits of those who have not yet embarked on their sexuality are safer; pregnancy choices for women who are infected; and a vaccine, obviously, as the long-term answer.

—CONSTANCE B. WOFSY, MD

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Medical Progress

Modern Neurosyphilis—A Critical Analysis

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Neurosyphilis remains a source of perplexity for today's physicians. Controversies exist over the interpretation of serologic tests, cerebrospinal fluid (CSF) abnormalities, diagnostic criteria, and treatment regimens. Its occurrence with human immunodeficiency virus (HIV) infection has raised fears of its recrudescence. A critical analysis of the evidence behind these viewpoints leads to several conclusions: the CSF VDRL is the most appropriate diagnostic test; pleocytosis is the only reliable CSF measure of disease activity; commonly accepted diagnostic criteria do not exclude nonsyphilitic disease; and treatment requires the prolonged use of parenteral penicillin, but no superior regimen has been found. Most data do not currently support the view that concurrent HIV infection produces accelerated or resistant neurosyphilis.

(Jordan KG: Modern neurosyphilis—A critical analysis. West J Med 1988 Jul; 149:47-57)

Despite its antiquity, syphilis, particularly as it affects the central nervous system, is still a source of uncertainty. Although *Treponema pallidum* was identified as the cause of general paresis more than 70 years ago,[1] the modern approach to neurosyphilis can be a confounding and controversial exercise. This is reflected in debated examples of "modified" neurosyphilis,[2] dilemmas over serologic interpretation,[3] and disagreements over appropriate therapy.[4] The presence of neurosyphilis in patients with the human immunodeficiency virus (HIV) has recently raised new questions.[5] Many physicians today are unfamiliar with neurosyphilis, a now uncommon, though not rare, disease. Its appearance in distinct stages and our dependence on serologic rather than bacteriologic findings add to clinicians' unease. The purpose of this review is to clarify some of the confusion by critically analyzing the main areas of controversy. These include serologic and bacteriologic tests for diagnosis, cerebrospinal fluid (CSF) abnormalities, modern diagnostic criteria, treatment, and concurrent HIV infection.

Serologic and Bacteriologic Tests for Diagnosis

Cerebrospinal Fluid Nontreponemal (Lipoidal) Antibody Tests

Shortly after *T pallidum* invades an organism, its interaction with host tissues produces a heterogeneous population of antibodies called reagins. In the classic studies on neurosyphilis,[6-9] the most commonly applied serologic test for detecting reagins was the Wassermann, in which extracts from the livers of syphilitic newborns were used to fix complement.[10] The Wassermann, however, proved to be the least sensitive of the nontreponemal antibody tests.[10,11] It was replaced in 1953 by the Kolmer, a far more sensitive complement fixation test, and later by the VDRL test. The VDRL depends on a flocculation reaction and not the fixation of complement (Figure 1).[12] In general, flocculation tests are more sensitive for detecting reagin antibodies. The relatively large immunoglobulins that produce the flocculation reaction do not readily fix complement, and the smaller immunoglobulins that do cause complement fixation require additional factors.[10] The modern VDRL antigen suspension has been made more sensitive by the use of purified cardiolipin-lecithin-cholesterol antigen plus choline chloride.[13] The VDRL slide test allows screening to be done on unheated specimens of serum, plasma, or CSF, while the rapid plasma reagin circle card and the automated reagin test provide mass screening techniques.[13]

To gauge neurosyphilitic activity, the CSF VDRL is quantified by measuring the dilution at which the test becomes unreactive. After adequate therapy, the CSF VDRL commonly becomes negative over 6 to 12 months. Occasionally, however, it will remain reactive at a 1:1 or 1:2 titer with otherwise adequate evidence of cure.[11] This tendency to reflect disease activity is an advantage of the VDRL over treponemal antibody tests, which remain reactive regardless of the state of disease.[11,14,15]

Many authors are reluctant to rely on the CSF VDRL for diagnosing active neurosyphilis because they consider it too insensitive.[16-18] The reported incidence of "false-negativity"—a nonreactive test in a patient with active neurosyphilis—ranges from 39%[19] to 60%.[20] This commonly held view appears based on three assumptions. The first is that the classic CSF Wassermann test, reported as nonreactive in 14% of cases of syphilitic meningitis, 19% of cerebrovascular syphilis, and 28% of tabes dorsalis,[8] possessed a sensitivity comparable to today's CSF VDRL. In fact, a comparison using an early method found the VDRL to be at least 24 times more sensitive than the Wassermann test (Table 1).[11] Modern refinements in the VDRL have further improved its sensitivity.[13]

The second assumption is that the classic studies excluded nonsyphilitic diseases among their seronegative patients. When these investigations were carried out in the 1920s and 1940s, many diseases known today were not yet recognized. As Fishman has pointed out,[21] the studies by Merritt and co-workers on cerebrovascular syphilis were done before the recognition of extracranial carotid artery disease, basilar ar-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
CNS = central nervous system
CSF = cerebrospinal fluid
FTA = fluorescent treponemal antibody [test]
FTA-ABS = fluorescent treponemal antibody absorption [test]
HIV = human immunodeficiency virus
MHA-Tp = microhemagglutination [assay for] *Treponema pallidum*
RIT = rabbit infectivity test

tery insufficiency, cerebral arteritis, and the lacunar syndromes.[8] Simon has similarly suggested that viral meningoencephalitis was not yet recognized.[22] These authors have argued that a patient with one of these disorders presenting in that era with a reactive blood Wassermann test, a nonreactive CSF Wassermann, and nonspecific CSF findings would understandably be assumed to have cerebrovascular or acute meningeal syphilis. Merritt and colleagues acknowledged the likelihood of nonsyphilitic disease being present in cases of "seronegative" cerebrovascular syphilis,[8] and this may also explain the paradox of "seronegative" meningeal syphilis. It is possible that other recently recognized conditions such as normal pressure hydrocephalus and paraneoplastic neurologic syndromes[23] were occasionally included in this category.

The third assumption is that the CSF VDRL is "less sensitive" than the CSF fluorescent treponemal antibody (FTA) test (or the microhemagglutination assay for *T pallidum*). These tests, however, measure completely different antibody populations. It is, therefore, inappropriate to compare their sensitivities with each other. The appropriate question is whether detecting reagin antibodies or antitreponemal antibodies is the more sensitive way to detect active neurosyphilis. Antitreponemal antibodies do not correlate with disease activity, while reagin antibodies do, reflecting the invasiveness of the spirochete in host tissues.[10,13] Antitreponemal antibodies may reflect only the presence of *T pallidum* proteins.[24,25]

The high specificity of a reactive CSF VDRL is widely acknowledged.[12,15,24] False-positive reactions may, however, occur when blood contaminates the CSF or in the presence of a substantially elevated CSF protein, paraproteinemia, or autoimmune disease.[26] These results can be clarified by a blood treponemal antibody test, which will confirm or refute that *T pallidum* infection has occurred.

Cerebrospinal Fluid Treponemal Antibody Tests

The CSF FTA technique was described in 1960 (Figure 2),[27] and subsequent investigators confirmed that it detects antibodies against *T pallidum* six times more readily than the CSF VDRL detects reagin antibodies.[20,28-30] Some have suggested modifications to detect early immunoglobulin M antitreponemal antibodies with equivocal results.[31,32] "Absorbing" the CSF eliminates nonspecific antibodies and improves specificity, but the dilution required greatly reduces the test's sensitivity.[20]

Although the CSF FTA test has been reported as reactive in 80% to 100% of cases of neurosyphilis,[3,20,29,33] its meaning and clinical usefulness have been challenged.[3,33-35] As little as 0.8 μl of blood in 1 ml of spinal fluid can cause a false-positive CSF FTA.[36] Interpretation, therefore, should be made with caution if erythrocytes are present, even if no blood is visible. A true-positive CSF FTA test is always associated with a reactive serum FTA-absorption (FTA-ABS) test and may merely reflect passive diffusion of serum antibodies into the CSF.[37] False-positive reactions have occurred in autoimmune disease, hypergammaglobulinemias, and in certain normal persons.[13] The Centers for Disease Control (CDC) have recommended that the CSF FTA test not be used.[34] Other authors disagree and rely on the test as an important diagnostic tool.[16,19,38,39]

The CSF microhemagglutination assay for *T pallidum* antibodies (MHA-Tp) is an agglutination reaction of sheep erythrocytes with absorbed *T pallidum* antigen (Figure 3). The CSF MHA-Tp can be titered and applied to multiple specimens more readily than can the CSF FTA test. The two have equal sensitivity and specificity,[40] but it is not clear if they detect the same antibodies.

The CSF *T pallidum* immobilization test, once the "reference" antitreponemal antibody test, depends on immobilized viable *T pallidum* in the presence of antibody and complement. It is a technically difficult and expensive test that pro-

TABLE 1.—*Comparative Reactivity of Serum Wassermann and VDRL Tests (341 Patients)**†

	Congenital Syphilis, Positive		Neurosyphilis, Positive		Other Definite Syphilis, Positive	
Test for Syphilis	*No.*	*Percent*	*No.*	*Percent*	*No.*	*Percent*
Wassermann	1	3	1	2	0	0
VDRL	25	68	27	48	55	43

*After Aho et al.[11]
†Patients were treated 10 to 17 years earlier with the use of heavy metals or as much as 9.0 million IU penicillin.

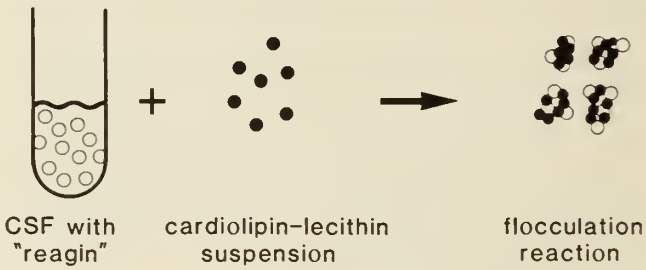

Figure 1.—The drawing illustrates the cerebrospinal fluid (CSF) VDRL test. Flocculation occurs when the "reagin" immunoglobulins link cardiolipin-lecithin-coated particles.

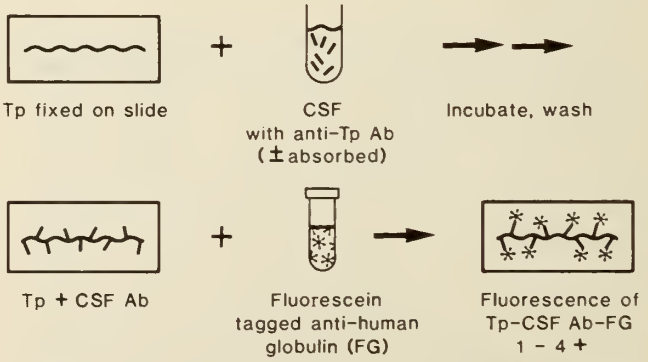

Figure 2.—The drawing illustrates the cerebrospinal fluid (CSF) fluorescent treponemal antibody test with and without absorption. (Absorbed indicates CSF treated with "sorbent" to remove "nonspecific" proteins and immunoglobulins.) Fluorescein-tagged anti-human globulin identifies antitreponemal antibodies (Ab) attached to prepared and fixed *Treponema pallidum* (Tp) organisms. The degree of fluorescence is subjectively graded from 1+ to 4+.

vides no more additional information than the combined results of the CSF VDRL and FTA or MHA-Tp tests. Only two laboratories in the country still run this test, and the CDC no longer do it.[13]

Once reactive, antitreponemal antibody tests remain so indefinitely regardless of disease activity.[13,24] Therefore, a reactive CSF FTA may indicate adequately treated neurosyphilis, asymptomatic neurosyphilis, active neurosyphilis, or a false-positive reaction. Some studies have not distinguished among these possibilities.[16-20,41]

Bacteriologic Diagnosis of Neurosyphilis

Treponema pallidum's stringent nutrient requirements, susceptibility to oxygen toxicity, and need for a mammalian cell environment have frustrated attempts to culture it in vitro.[42] Darkfield microscopy and immunofluorescent staining of CSF have occasionally shown the organism.[43,44] In parenchymal neurosyphilis, silver staining has detected *T pallidum* in postmortem specimens[1,45] and in biopsy specimens[46] of cerebral cortex; meningeal or brain biopsies for diagnosis, however, are of uncertain reliability and rarely indicated.

The rabbit infectivity test (RIT), introduced in 1913,[47] is used today to recover *T pallidum* from infected tissue and to maintain viable organisms for research (Figure 4).[25,48,49] Early investigators used the RIT to identify *T pallidum* in human CSF. Table 2 summarizes their experience with neurosyphilis patients, most of whom had late disease of undefined activity. More recently, Tramont reported positive CSF rabbit infectivity tests in two patients,[43] and we recovered *T pallidum* in two cases of syphilitic meningitis.[50] The modern CSF RIT may be more sensitive because it uses strict temperature controls, regular testicular aspirations, sensitive serologic testing, and lymph node transfer techniques (Figures 5 and 6).[48,50] Table 3 presents results of an experiment to determine the sensitivity of the modern CSF RIT using FTA-reactive human CSF.[50,51] Inoculating only one to three organisms per testis produced serologic conversion or recovery of spirochetes (or both) in three of four rabbits. Inoculating ten or more *T pallidum* per testis produced 100% recovery. The high sensitivity of the CSF RIT, however, does not mean that a negative test rules out neurosyphilis in a donor. Spirochetes

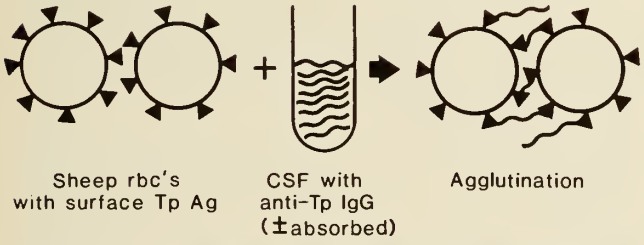

Figure 3.—The drawing illustrates the cerebrospinal fluid (CSF) microhemagglutination assay for *Treponema pallidum* antibodies. Antitreponemal (anti-Tp) immunoglobulins (IgG) bind to sheep erythrocytes (rbc's) with surface *T pallidum* antigen (Tp Ag) to produce hemagglutination.

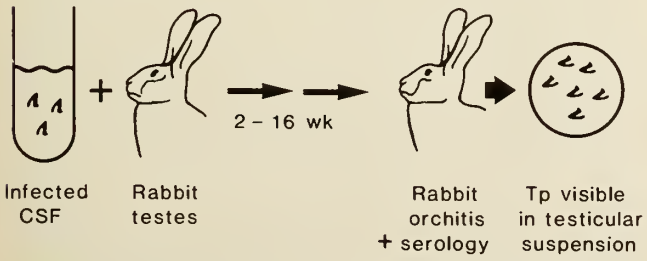

Figure 4.—The diagram illustrates the rabbit infectivity test. Inoculum of cerebrospinal fluid (CSF) containing sparse *Treponema pallidum* (Tp) injected into rabbit testes produces syphilitic orchitis with a large number of recoverable *T pallidum*.

Figure 5.—Preorchitic and orchitic states 19 days **(top)** and 34 days **(bottom)** after inoculation with 5 *Treponema pallidum* per testis (10 per ml) of Nichols's strain *T pallidum* diluted in fluorescent treponemal antibody-reactive human cerebrospinal fluid.

Figure 6.—A darkfield photomicrograph shows a pathogenic *Treponema pallidum* organism aspirated from the left testis shown in Figure 5 (preorchitic state) (original magnification × 3,750).

may be sequestered in the central nervous system parenchyma or meninges. In addition, *T pallidum* from syphilitic human CSF probably multiplies less actively than rabbit-adapted *T pallidum* and is coated with host antibody that may inhibit its reproduction in rabbit testes.[49] Acknowledging these limitations, historical precedent shows recovery of *T pallidum* organisms in 52% of patients mainly with late neurosyphilis of undefined activity. This detection rate may be higher when modern techniques are applied to active disease.

CSF Abnormalities

CSF Cell Count and Protein and Glucose Concentrations

Many authors consider the CSF cell count to be the best index of neurosyphilitic activity and a normal cell count to indicate inactive disease regardless of the clinical picture.[52-54] They also consider a protein level greater than 45 mg per dl consistent with active disease. Others claim that active neurosyphilis can be seen with an acellular spinal fluid and normal protein levels.[16,19,55,56] Dewhurst reported that 18 of 58 patients with syphilitic dementia had normal CSF counts.[56] He suggested that the widespread use of penicillin had modified the CSF profile seen in early studies. The CSF glucose level is low in 60% of cases of syphilitic meningitis, but usually remains normal in other forms of neurosyphilis.[8]

The CSF cell count and protein and glucose levels are nonspecific and by themselves can never be taken as diagnostic of neurosyphilis. Controversy over the CSF profile in neurosyphilis reflects a fundamental disagreement over the diagnostic criteria for the disease (see "Diagnostic Criteria").

TABLE 2.—*Previous Use of Cerebrospinal Fluid Rabbit Infectivity Test in Human Neurosyphilis*

Investigator, Year	*Syphilitic Syndrome*	*Patients, No. Positive/ No. Reported*
Early cases*		
Volk, 1913	General paresis	1/5
Nichols and Hough, 1913	"Recurrent neurosyphilis"	1/1
Arzt et al, 1914	General paresis	2/6
	Tabes dorsalis	2/3
Marinesco and Minea, 1914	Juvenile general paresis	1/1
Fruhwald and Zaloziecki, 1916	Secondary	3/8
	General paresis	1/3
Wile, 1917	General paresis and tabes dorsalis	5/8
Recent cases		
Tramont, 1976[43]	Latent	1/1
	Secondary	1/1
Jordan and Daviau, 1979[50]	Meningitis	2/2
Total positive 20/39=52%		

*Data from Chesney and Kemp.[47]

TABLE 3.—*Cerebrospinal Fluid (CSF) Rabbit Infectivity Test Using FTA-Reactive Human CSF and Nichols's Strain* Treponema pallidum *(Tp)*

*Rabbit Group**	*Mean No. of Tp Inoculated per Testis*†	*Days to Positive FTA-ABS*	*Days to Positive Aspiration*	*Days to Clinical Orchitis*‡
1A	200	26	19	21
1B	100	18	17	24
1C	200	19	19	24
2A	20	40	28	31
2B	10	30	28	40
2C	20	40	24	28
2D	10	30	28	30
3A	2.0	ND	33	35
3B	1.0	NR	Neg	NR (70)§
3C	2.0	40	ND	31
3D	1.0	40	40	NR (44)§

FTA=fluorescent treponemal antibody, FTA-ABS=FTA absorption, NO=not done, NR=nonreactive

*Group A: injected with 1+ reactive CSF-FTA suspension, Group B: injected with 4+ reactive CSF-FTA suspension; Groups C and O: injected with unreactive CSF-FTA *T pallidum* suspension.

†Calculated with the enumeration method of Magnuson et al.[51] Fractional values were rounded off to the highest integer; standard deviation=11.3%.

‡Final *T pallidum* count for all orchitic testes $>1.0\times10^5$/ml

§The numbers in parentheses indicate days observed.

CSF γ-Globulin

An elevated γ-globulin level to more than 13% of the total CSF protein is found in 70% of cases of neurosyphilis[57] but is also a common finding in patients with multiple sclerosis, the Guillain-Barré syndrome, vasculitis, chronic meningitis, and subacute sclerosing panencephalitis. It remains elevated for at least 12 years in 35% of cases, regardless of disease activity.[55] Its value in diagnosing active neurosyphilis is limited: a normal value does not rule it out, and an elevated value does not mean active disease.

CSF Oligoclonal Bands and Intrathecal Antitreponemal Antibody

Abnormal CSF oligoclonal bands are often present in patients with neurosyphilis and contain intrathecally produced antitreponemal antibodies.[58,59] There is debate whether oligoclonal immunoglobulin G patterns change in response to therapy. Vartdal and associates reported no change eight months after treatment,[59] while Mazzarello and colleagues reported a reduction or disappearance of bands in two patients.[60] As a diagnostic test, however, oligoclonal bands are as nonspecific as γ-globulin levels. There is no convincing evidence that abnormal bands or intrathecal antitreponemal antibodies signify active neurosyphilis.[59,61]

Therapeutic Response

It has been suggested that following treatment, objective clinical improvement or an increase in the CSF leukocyte count—"provocative pleocytosis"—can confirm the diagnosis of active neurosyphilis.[7,8,16] In a given case, however, it

TABLE 4.—*'Modern' Criteria for Diagnosing Neurosyphilis*†

1. Positive serum fluorescent treponemal antibody (absorption) test (FTA-[ABS])
2. Ophthalmic or neurologic findings "suggestive" or "diagnostic" of neurosyphilis
3. Positive CSF FTA(ABS) with >5 leukocytes/μl or protein >40 mg/dl
4. Positive CSF FTA(ABS) in patients with progressive neurologic symptoms in whom other causes were ruled out, *plus*

   Increased CSF leukocyte count after penicillin treatment—provocative pleocytosis

   or

   Improvement after penicillin treatment

CSF=cerebrospinal fluid

*From Hooshmand et al,[16] Kolar and Burkhart,[19] Joyce-Clarke and Molteno,[38] and Hotson.[39]

†Active neurosyphilis is diagnosed in the presence of numbers 1 and 2, 1 and 3, or 1 and 4. A reactive CSF VORL is not required.

may be hard to distinguish improvement following therapy from improvement because of therapy. Patients with nonsyphilitic diseases such as atherosclerotic cerebral infarction or viral meningoencephalitis often improve spontaneously. Symptoms and signs of neurosyphilis may stabilize but not resolve following adequate treatment.[8,62] Vascular and parenchymal neurosyphilis may progress despite curative doses of penicillin.[62,63] In any meningeal inflammatory process, lumbar CSF leukocyte counts may fluctuate,[64] and it seems wise to interpret the notion of a provocative pleocytosis with caution; it has never been subjected to a controlled study.[64,65]

Diagnostic Criteria

'Modern' Criteria for Neurosyphilis

Table 4 is a composite list of "modern" diagnostic criteria for active neurosyphilis. A reactive CSF VDRL has been omitted because it is not required by any of the authors. Close examination of these criteria reveals several limitations.

A positive serum FTA-ABS (or MHA-Tp) indicates a past systemic treponemal infection but does not imply active disease or central nervous system (CNS) involvement.[3,24] Because a reactive FTA-ABS persists indefinitely[13] and symptomatic neurosyphilis develops in only 6.5% to 30% of infected, untreated patients,[8,66] a positive test is far more likely to be found in the absence than in the presence of neurosyphilis.[34] Signs "suggestive of neurosyphilis" are unhelpful because the clinical findings in more common neurologic diseases, such as atherosclerotic cerebral infarction, hypertensive vasculopathy, CNS infections, parameningeal tumors, or peripheral neuropathies, overlap with the signs of neurosyphilis, preventing reliable inferences.[34] In addition, signs "typical" of neurosyphilis, such as Argyll Robertson pupils or sensory ataxia, may reflect past neurologic injury unrelated to the patient's present problem. A CSF FTA reaction may merely reflect diffusion of serum antibodies[37] and, like the serum FTA-ABS test, does not reflect disease activity. CSF pleocytosis and protein elevation have limited value because many neurologic diseases, most of them more common today than neurosyphilis, cause these changes. The limitations of drawing conclusions from a provocative pleocytosis or a response to therapy have been discussed ("CSF Abnormalities"). Diagnosing neurosyphilis by exclusion is

TABLE 5.—*The Cerebrospinal Fluid (CSF) Rabbit Infectivity Test (RIT) in Patients Fulfilling 'Modern' Criteria for Active Neurosyphilis*

			Serum		CSF					CSF-RIT			
Patient	Age,yr	Sex	VDRL	FTA-ABS	VDRL	FTA	Formula	Past Syphilis	Syndrome	Sero-conversion	Tp Recovery	LNT	Observation Time, mo
1 . . .	63	♂	1:4	2+	NR	1+	WBC 8,* PR 65†	No	Rt hemiparesis, hypertension	Neg	Neg	. . .	4
2 . . .	22	♂	NR	4+	NR	4+	WBC & PR normal	Rash 9 yr ago, no therapy	Depression, delusions	Neg	Neg	. . .	4
3 . . .	71	♂	NR	3+	NR	3+	. . .	PNC 1970	AR pupil, facial dyskinesia	Neg	Neg	. . .	4
4 . . .	89	♂	NR	2+	NR	2+	WBC 6, PR 61	Possible	Dementia for 2 yr	Neg	Neg	Neg	8
5 . . .	70	♂	NR	4+	NR	4+	WBC & PR normal, γglob ↑	None	Dementia for 2 yr	Neg	Neg	Neg	8
6 . . .	48	♂	NR	1+	NR	1+	IgG↑, PR 90	None	Diabetes mellitus, irregular pupils	Neg	Neg	Neg	8
7 . . .	65	♀	NR	3+	NR	2+	WBC & PR normal	PNC 1950	Rt T-6 root pain	Neg	Neg	Neg	8
8 . . .	50	♂	1:4	3+	NR	3+	. . .	PNC 1948	Chronic anemia, irregular pupils	Neg	Neg	Neg	8
9 . . .	37	♀	1:64	3+	1:8	3+	WBC 140, PR 80	None	Syphilitic meningitis	Pos	Pos	. . .	4
10 . . .	52	♂	NR	2+	NR	1+	WBC 0, PR 38	None	L-5 root pain, abnormal myelogram	Neg	Neg	Neg	8
11 . . .	65	♀	Reactive‡	3+	NR	1+	WBC 0, PR 68	None	Confusion, pulmonary fibrosis	Neg	Neg	Neg	8
12 . . .	67	♂	1:8	1+	NR	1+	WBC 0, PR 72	None	Cirrhosis, lethargy, irregular pupils	Neg	Neg	Neg	8
13 . . .	64	♂	NR	1+‖	NR	2+	WBC 0, PR 130, γglob 11.7%	None	Guillain-Barré syndrome	Neg	Neg	Neg	8
14 . . .	6	♀	NR	1+	NR	1+	WBC 0, PR 20, γglob 17%	None	Cerebral palsy, new brain-stem signs	Neg	Neg	Neg	8
15 . . .	69	♂	NR	2+	NR	2+	WBC 6, PR 24	Heavy metal 1930, PNC 1945	Breast cancer 1977, bilateral hand numbness	Neg	Neg	Neg	8
16 . . .	33	♂	1:32	3+	NR	2-3+	WBC 1, PR 46, γglob 14%	Chancre 2 mo before PNC, 1 mo before RIT	Poor pupil reaction, ↑ left deep tendon reflexes	Neg	Neg	Neg§	5
17 . . .	20	♂	NR	3-4+	1:2	1+	WBC 3,000, PR 282, glucose 81,† cultures neg	No, 24 mil units PNC before RIT	Confusion, meningeal signs	Pos	Neg	Pos	5
18 . . .	58	♂	NR	2-3+	NR	1+	WBC 0, PR 40, γglob 18%	None	Seizure 1979, transient deafness left ear 1982	Neg	Neg	Neg	4

AR=Argyll Robertson, FTA=fluorescent treponemal antibody (test), FTA-ABS=FTA absorption (test), γglob=γ-globulin, IgG=immunoglobulin G, LNT=lymph node transfer, Neg=negative, NR=nonreactive, PNC=penicillin, Pos=positive, PR=protein, Tp=*Treponema pallidum*, WBC=leukocytes, ↑=increased

*Per microliter.
†Milligrams per deciliter.
‡Rapid plasma reagin test.
§After one month.
‖Borderline reading.

TABLE 6.—*Nonsyphilitic Diagnoses in Patients Reactive to Cerebrospinal Fluid (CSF) FTA With Negative CSF-Rabbit Infectivity Tests*

Patient	Age,yr	Sex	Syndrome	Neurosyphilis Diagnosis	Alternate Diagnosis	Course
1 . . .	63	♂	Right motor hemiparesis, hypertension	Cerebrovascular syphilis	Late-latent lues and lacunar infarction	IV penicillin; improved
2 . . .	22	♂	Depression, delusions	Juvenile general paresis	Treated lues and endogenous depression	IV penicillin; no change
3 . . .	71	♂	AR pupil, facial dyskinesia	General paresis	Treated lues and Meige's disease	IV penicillin; no change
4 . . .	89	♂	Dementia for 2 yr	General paresis	Treated or late-latent lues and Alzheimer's disease	IV penicillin; no change
5 . . .	70	♂	Dementia for 2 yr	General paresis	Late-latent lues and Alzheimer's disease	IV penicillin; no change
6 . . .	48	♂	Diabetes mellitus, irregular pupils	Asymptomatic	Late-latent or no lues, diabetes mellitus	No penicillin
7 . . .	65	♀	Right thoracic root pain	Syphilitic radiculitis	Treated lues and thoracic DJD	Nerve block; improved
8 . . .	50	♂	Chronic anemia, irregular pupils	Asymptomatic	Treated lues and chronic AIHA	No change

AIHA=autoimmune hemolytic anemia, AR=Argyll Robertson, DJO=degenerative joint disease, FTA=fluorescent treponemal antibody, IV=intravenous

circular because such exclusion depends on the diagnostic criteria applied and will be limited by a physician's resources or resourcefulness.[8,34]

Because of their limitations, these criteria cannot distinguish nonsyphilitic neurologic disease in the presence of inactive syphilis from active neurosyphilis. This may encourage the misperception that nonsyphilitic disease is neurosyphilis[18,34] and lead to an unnecessary hospital admission with penicillin administration. There is the concomitant risk of a delayed diagnosis of nonsyphilitic disease.

Supporting these concerns are our results using the CSF RIT in 18 patients who fulfilled these criteria (Table 5). All patients had reactive CSF FTA and serum FTA-ABS tests. Serum VDRLs were reactive in six, but only two patients had reactive CSF VDRLs. Five had altered mental states; five had abnormal pupillary reactions, including one with Argyll Robertson pupils; two suffered nerve root syndromes; and one each presented with hemispheric stroke, acute hearing loss, brain-stem dysfunction, a Guillain-Barré-like syndrome, psychotic depression, and facial dyskinesia.

Only the two patients with reactive CSF VDRLs and significant CSF pleocytosis had recoverable *T pallidum,* confirming active neurosyphilis. Of the other 16, the rabbits of 12 underwent lymph node transfers with a total observation time of eight months. As discussed, limitations inherent to this technique prevent definitive conclusions, but the results suggest that patients without reactive CSF VDRLs or significantly elevated CSF cell counts, although fulfilling modern criteria, do not have confirmable active neurosyphilis. A follow-up study on eight of these patients found that their active neurologic illnesses were nonsyphilitic (Table 6).

This analysis suggests that in the absence of a positive CSF VDRL and pleocytosis, active neurosyphilis should be diagnosed with circumspection and only after a thorough search for alternative explanations. This view is held by several authorities.[21,22,29] A reactive serum FTA-ABS test is necessary to establish that the CSF VDRL is not a false-positive test. Greater than 5 leukocytes per μl is generally considered an indication of active neurosyphilis.[22,53] In our series, however, three patients with 6 to 8 leukocytes per μl had negative infectivity tests. Recommended criteria are summarized in Table 7. In the presence of neurologic signs and symptoms, patients meeting these should be diagnosed as having active neurosyphilis. Those without neurologic signs and symptoms have asymptomatic neurosyphilis.

Asymptomatic neurosyphilis and nonsyphilitic neurologic disease may occasionally coexist. In this dilemma, further neurodiagnostic studies and empiric therapy may be necessary. In rare cases the clinical context will not permit a negative CSF VDRL to exclude active neurosyphilis. In a patient with a progressive neurologic disorder consistent with a recognized form of neurosyphilis, a reactive serum FTA-ABS, CSF pleocytosis, and no alternative diagnosis, a nonreactive CSF VDRL should not prevent prudent empiric treatment for "possible" neurosyphilis. Diagnostic inquiry should remain active, however, because the continued search for a nonsyphilitic explanation may be rewarded. In a patient with progressive neurologic deficits, a reactive serum FTA-ABS test, and completely normal cerebrospinal fluid, the diagnosis of active neurosyphilis remains highly unlikely and decisions to treat become harder to justify. A nonsyphilitic illness is usually responsible.[22,53,67]

TABLE 7.—*Recommended Criteria for Diagnosing Active Neurosyphilis**

A reactive modern cerebrospinal fluid (CSF) VDRL test; the results should be quantified (a blood VDRL may or may not be reactive)

A reactive blood FTA-ABS test—this establishes that the CSF VDRL is not a biologically false-positive reaction

CSF pleocytosis greater than 5 leukocytes/μl—most cases will also show CSF protein level greater than 45 mg/dl

FTA-ABS=fluorescent treponemal antibody absorption

*All criteria are required for a firm diagnosis. Under certain circumstances, an unreactive CSF VDRL may be consistent with a diagnosis of "possibly active neurosyphilis." See text.

'Modified' Neurosyphilis

Recent reviews have described in detail the various stages and clinical features of classic neurosyphilis.[22,39] Several authors have suggested that "atypical" neurologic findings are more common today than the classic syndromes described in textbooks.[16,18] Hooshmand and co-workers popularized the concept of "modified" neurosyphilis.[16] They reviewed 241 cases and found the presenting symptoms to be seizures in 58, stroke in 27, dizziness in 19, personality changes in 9, and cervical spondylosis in 9. Luxon and associates described 17 cases presenting with otologic, ophthalmologic, and atypical myelopathies.[68] Joffe and colleagues reported seven diagnostically difficult cases with vertebrobasilar syndromes, cervical spondylosis, and behavioral changes.[2] Other investigators have reported similar atypical findings.[18,19,38]

The manifold presentations of cerebrovascular, meningovascular, pachymeningeal, tabetic, and paretic syphilis are simplified in texts for heuristic reasons.[8] Vascular neurosyphilis has become comparatively more common[18,69,70] because parenchymal neurosyphilis has been virtually eradicated by successful public health measures.[68-71] None of the clinical findings or syndromes described in cases of modified neurosyphilis, however, are unusual or new.[72] Luxon and co-workers point out that these had been reported in the preantibiotic era.[68] Some cases of modified neurosyphilis may represent nonsyphilitic disease.[22,34]

Treatment

Mechanism of Penicillin Action

Penicillin inhibits treponemal transpeptidases, which catalyze the synthesis of precursors of a mucopeptide (peptidoglycan) responsible for stability of the spirochete's cell wall. During growth and division, cytoplasmic lysozymes damage this barrier, which must be repaired to prevent destruction of the treponeme by osmotic pressure.[73] Because *T pallidum* divides only every 33 hours, prolonged treponemicidal concentrations are necessary. Interrupted enzyme inhibition for as little as 20 minutes may allow renewed transpeptidase activity and *T pallidum* survival.[73]

Unlike many other microorganisms, *T pallidum* has retained its sensitivity to penicillin.[73] Early syphilis is treated successfully with serum levels of only 0.02 μg per ml. A concentration of 0.1 μg per ml produces maximal treponemal immobilization in vitro, and lesions in experimental syphilis resolve rapidly with levels of 0.4 μg per ml.[74] The World Health Organization recommends maintaining a serum penicillin concentration of not less than 0.031 IU per ml (0.018 μg per ml) for 7 to 15 days for early syphilis and longer for late syphilis.[66,73]

Treatment of Early Syphilis

Several case reports describe early syphilis progressing to neurosyphilis despite treatment with recommended doses of penicillin.[75-77] In most of these, it is difficult to exclude reinfection as an alternative explanation. Bayne and colleagues, however, reported a persuasive case of a patient who underwent peripheral serologic cure within four months of conventional treatment for secondary syphilis, and then acute syphilitic meningitis developed.[76] Standard therapy for early syphilis of 2.4 million units of intramuscular benzathine penicillin G given once—some authorities repeat this dose a week later[78]—has produced seronegativity, resolved clinical symptoms, and prevented late progression in the vast majority of patients.[79] Follow-up studies show that 3½ decades after proven infection and treatment, none of 88 subjects had clinical evidence of late syphilis. Similarly, no late symptoms were identified in 173 patients who had lived for more than 20 years after treatment of their early infection.[79] Of 151 CSF examinations done two to eight years after conventional treatment of early syphilis, all were normal except one that had a protein level of 60 mg per dl. All patients were asymptomatic.[80] In view of these data, many authorities consider lumbar puncture unnecessary in neurologically normal patients with early syphilis.[81-84] Recommended treatment does not guarantee outcome, however; clinical and serologic follow-up care remains indispensable.

Penicillin Regimens for Neurosyphilis

Other studies question the conventional penicillin doses for active neurosyphilis: subtreponemicidal CSF penicillin concentrations have been reported[4,85-87]; *T pallidum* has been recovered from treated patients,[25,43,49] and progressive neurosyphilis has been described after high-dose therapy.[55,56] Some of these reports contain methodologic errors. In 12 patients treated with intramuscular benzathine penicillin G, no detectable levels of penicillin were found in the CSF, but a lumbar puncture was done immediately after the penicillin was administered, giving insufficient time for CSF transport to occur.[86] Several studies included patients without convincing evidence of active neurosyphilis or meningeal inflammation.[85,88,89] Wiesel and associates, noting the high cure rate of neurosyphilis with benzathine penicillin G, suggested that the mechanism for cure is unrelated to CSF penicillin levels.[90] In fact, no direct relationship has yet been established between CSF penicillin concentrations, CNS tissue concentrations, and the outcome of therapy.[89] Others have shown that sublethal concentrations of antibiotics can allow intrinsic host defenses to cure the infection.[74]

Organisms resembling *T pallidum* have been found after high-dose penicillin therapy.[25,45,49,91] Published infectivity tests used human lymph nodes or rabbit tissue and may not be applicable to human neurosyphilis.[25,28] These studies suggest that, after adequate penicillin treatment, *T pallidum* forms can be transmitted from human and animal tissue. These organisms are morphologically altered, less infective, and appear nonvirulent. Their persistence does not indicate active syphilis: clinical cure may correspond to the organisms' loss of pathogenicity rather than total spirochetal destruction. These nonvirulent *T pallidum* may account for persisting antitreponemal antibodies found in treated patients.[25] Only two studies examined human CNS tissue using darkfield microscopy to detect rare *Treponema*-like forms of uncertain viability in the brain and spinal fluid.[45,49]

Progression of late neurosyphilis following therapy[55,56,92] may have limited relevance today given the rarity of general paresis and tabes dorsalis.[70,71] Of 100 patients with general paresis, 39% had new neurologic signs develop over an average of 12 years following treatment.[91] Seizures and strokes occurred most frequently. Another review of 43 patients under hospital care for 20 years with general paresis found a 65% incidence of new localizing signs or defects of higher cortical function.[55] This high incidence of neurologic progression was not necessarily due to active neurosyphilis—that is, it may have reflected nonsyphilitic disease, residual cerebrovascular injury, reinfection, or ongoing autoimmune injury.[72,93] A controlled population matched for age and severity of illness might also show a high incidence of acquired neurologic symptoms if followed for one to two decades. When parenchymal neurosyphilis was more widespread, permanent damage before treatment commonly occurred.[62] Dewhurst reported complete recovery in only 9% of patients with paresis, with irreversible damage causing death or confinement to an institution in 45%.[56]

While these studies do not prove the inadequacy of previously recommended treatment schedules, concern over them has led to revised guidelines.[94] The Centers for Disease Control now suggest one of three "potentially effective regimens," shown in Table 8, acknowledging that "none has been adequately studied." My preference is to treat for a longer

duration and to avoid benzathine penicillin G therapy that has failed to cure active neurosyphilis (Table 9).[95] Aqueous penicillin G, 4 million IU given intravenously at four-hour intervals, produces CSF penicillin concentrations of 0.31 IU per ml, ten times the accepted treponemicidal level.[87] Among eight patients treated with 3 million IU of penicillin given intravenously at four-hour intervals, trough serum and CSF levels reached a nadir of only 3½ times the treponemicidal level.[96] The authors suggested that an interdose interval of longer than four hours might allow concentrations to fall to subtreponemicidal levels. The use of probenecid has been shown to increase CSF penicillin concentrations when combined with various regimens.[88,89]

Whichever regimen is chosen, careful follow-up is necessary to ensure a cure. CSF examinations for cell count, protein and glucose levels, and quantitative VDRL titers should be done at 6 weeks and at 3, 6, 12, and 24 months after treatment. The guidelines of Dattner and colleagues for interpreting CSF changes[67] are generally considered authoritative.[22,52] A falling leukocyte count is the earliest indication of CSF improvement. It should decline serially to normal—less than 4 to 5 leukocytes per μl—within six months. CSF protein levels tend to fall more slowly, taking as long as two years to return to normal. Sustained normal cell counts reflect inactivation of the infection. If a relapse occurs, it is usually heralded by an increasing CSF cell count and occurs within two years of treatment. An apparent relapse later than this is usually due to reinfection. An initially high CSF VDRL titer is expected to decline fourfold within a year. When titers are persistently low, one retreatment course may be advisable. If there is no CSF pleocytosis and the VDRL titer does not increase, additional treatment is unlikely to be of value.[97] A fourfold increase in the serum or CSF VDRL titer probably indicates reinfection and the need for retreatment.

TABLE 8.—*Centers for Disease Control Treatment Regimen for Active Neurosyphilis**

Potentially effective regimens, none of which have been adequately studied, include

Aqueous crystalline penicillin G, 12 to 24 million units IV/d—2 to 4 million units every 4 h—for 10 d, followed by benzathine penicillin G, 2.4 million units IM/wk for 3 doses

or

Aqueous procaine penicillin G, 2.4 million units IM/d, plus probenecid, 500 mg by mouth 4 times/d, both for 10 d, followed by benzathine penicillin G, 2.4 million units IM/wk for 3 doses

or

Benzathine penicillin G, 2.4 million units IM/wk for 3 doses

IM=intramuscular, IV=intravenous

*From Centers for Disease Control.[94]

TABLE 9.—*Preferred Treatment Regimen for Active Neurosyphilis*

Diagnosis	*Treatment*
Acute and subacute neurosyphilis—inpatient*	Aqueous crystalline penicillin G, 4 million units IV every 4 h for 21 d
Indolent neurosyphilis—outpatient†	Aqueous procaine penicillin G, 2.4 million units IM on alternate days for 20 d (10 doses), plus probenecid, 500 mg by mouth 4 times/d
	Measuring trough cerebrospinal fluid penicillin concentrations 5 d after therapy started may be useful; desired level ≥0.031 IU/ml

IM=intramuscular, IV=intravenous

*Syphilitic meningitis; cerebrovascular syphilis.

†Asymptomatic neurosyphilis; parenchymal neurosyphilis. Failure of intramuscular treatment should be followed by intravenous regimen.

Penicillin Allergy

Patients who are allergic to penicillin face no well-established alternative therapy. Tetracycline, erythromycin, cephalosporins, and chloramphenicol possess antitreponemal activity, but their use in neurosyphilis is based on unexamined clinical experience.[62] Penicillin allergy, therefore, must be unequivocally confirmed by history or skin testing. With confirmed allergy, particularly in the presence of acute disease, consideration should be given to desensitization. Chloramphenicol has been the traditional alternative, but cefuroxime has proven treponemicidal activity[73] and enters the spinal fluid sufficiently to be used in cases of bacterial meningitis. Some of the third-generation cephalosporins may also prove useful.[62,63]

Jarisch-Herxheimer Reaction

Shortly after therapy is initiated, some patients suffer chills, myalgias, fever, and occasionally an exacerbation of neurologic abnormalities. This is the Jarisch-Herxheimer reaction. Treponemal lipopolysaccharides liberated during therapy produce an endotoxemia responsible for the reaction.[97] Similar reactions have been reported in other spirochetal diseases. The Jarisch-Herxheimer reaction is uncommon, with a recently determined incidence of only 3%. Only 1 fatality in 1,086 patients has been reported.[62] It may be more likely to occur among patients with secondary syphilis who have high levels of spirochetes in the serum.[5] Corticosteroids have been used to prevent or ameliorate the reaction, but there are no controlled data supporting this practice.

Neurosyphilis and Concurrent HIV Infection

Neurosyphilis has been reported recently in five homosexual patients with concurrent HIV infection.[5,76,99] The coincidence of HIV and syphilis in this risk group is not surprising. The authors suggest, however, that neurosyphilis occurred in these patients with unexpected frequency, an unusually short latency, increased severity, and a reduced responsiveness to penicillin therapy.

Our understanding of the immunobiology of syphilis supports the concerns expressed by these authors. Humoral immunity does not protect the human host against syphilis, and the numerous demonstrable antibodies do not alter progression of the disease.[100,101] Cell-mediated immunity plays a more significant role.[101,102] It develops late in secondary syphilis and is manifested by the inability to reinfect with challenge inoculation. Lymphocytes from immune donors confer resistance to challenge inoculation, transform in the presence of treponemal antigen, and inhibit macrophage migration. With selective abolition of the cell-mediated immunity by cytotoxic drugs, syphilitic lesions multiply and disseminate, the incubation time is shortened, and healing is prolonged. There is a striking decrease in lymphocytic reaction at infected sites. These results suggest that syphilis may be a more aggressive disease in immunocompromised patients.

This anxiety must be tempered, however, by the preliminary nature of the clinical reports. All four of the patients in

the report by Johns and co-workers responded to intravenous penicillin therapy with at least a fourfold reduction in serum VDRL titers and a substantial improvement in CSF serologic findings and pleocytosis.[5] Their neurologic symptoms were not unusually severe: one patient suffered a facial palsy, one a mild hemiparesis, and one was asymptomatic. None had a "protracted or malignant course"[99]; in fact, all patients improved. The latency time to symptoms was not atypically short: the two patients diagnosed as having meningovascular syphilis, which usually has a latency of 3 to 12 years, had CSF and clinical features more consistent with acute syphilitic meningitis, which usually occurs within 2 to 10 months of the initial infection.[9,103]

Despite a voluminous number of articles,[104-106] there is little evidence implicating syphilis as a serious opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS). In a recent postmortem series, the CDC found no difference in the incidence of coexisting HIV infection between patients with progressive or arrested syphilis.[107] This does not support the hypothesis that HIV modifies syphilis infection. Male homosexuals are at risk for both diseases. Those whose behaviors expose them to HIV are more likely to be exposed to syphilis.[107] If an increased incidence of neurosyphilis were found in this group, it would not necessarily be on an immunologic basis. Societal antipathy towards AIDS victims[108] and personal ambivalence about HIV testing[109] might discourage gay men with early syphilis from seeking prompt medical attention, increasing their risk of later complications.

There is also concern that HIV infection may reduce the reliability of routine screening tests for syphilis. Hicks and colleagues reported the case of an HIV-positive patient with Kaposi's sarcoma and a generalized rash whose negative serum VDRL and FTA-ABS tests delayed the diagnosis of secondary syphilis.[110] Spirochetes were found using silver staining on a skin biopsy specimen. The VDRL and FTA-ABS tested reactive 20 days after the initially negative studies. The authors concluded that concurrent HIV infection, by rendering the immune response to *T pallidum* defective, may produce falsely negative serologic tests. In contrast, in a recent study, Schultz and colleagues found an equal incidence of rapid plasma reagin reactivity among MHA-Tp-positive homosexuals regardless of their HIV status.[111] It is possible that Hicks and co-workers' patient—who displayed delayed seropositivity, not seronegativity—may have presented during the seronegative interval that occurs in immunocompetent patients after the initial spirochete infection and that can last eight to nine weeks.[112] Manifestations of secondary syphilis may begin during this early stage despite initially negative VDRL and FTA-ABS tests in 24% and 14% of cases, respectively.[113]

These provocative reports emphasize the concerns that syphilis may be more virulent and harder to diagnose in HIV-infected patients. The weight of evidence does not currently support these views or suggest the need for a different treatment regimen. It is hoped that ongoing studies of patients coinfected with syphilis and HIV will further clarify this issue.[107]

Conclusions

Clinicians are justifiably confused by controversies over the diagnosis, clinical presentation, and treatment of modern neurosyphilis. A critical analysis of these issues leads to the following conclusions:

- The modern CSF VDRL test is currently the most appropriate diagnostic test for active neurosyphilis. Serum and CSF treponemal antibody tests provide evidence of past *T pallidum* infection, but they give no information about CNS activity.
- The degree of CSF pleocytosis is a useful indicator of disease activity. Other CSF findings in neurosyphilis are nonspecific. γ-Globulin, oligoclonal banding, and intrathecal antitreponemal antibodies are not reliable markers of active neurosyphilis.
- Modern criteria for neurosyphilis (Table 4) do not exclude nonsyphilitic disease and should not provide the basis for diagnosing active neurosyphilis. This diagnosis should depend on a reactive CSF VDRL, reactive serum FTA-ABS, and CSF pleocytosis. The specific neurosyphilitic syndrome is determined by historical and clinical findings. In certain contexts, a negative CSF VDRL may be consistent with a diagnosis of possible neurosyphilis.
- Many published cases of modified neurosyphilis represent clinical findings well described in the early literature on the disorder, while others may represent nonsyphilitic diseases.
- Primary and secondary syphilis should be treated with recommended doses of benzathine penicillin G, which has been established as preventing complications of late syphilis in the vast majority of patients. Reports to the contrary vary in persuasiveness but rightly emphasize the importance of follow-up care.
- The treatment of active neurosyphilis should produce uninterrupted CSF penicillin concentrations of no lower than 0.031 IU per ml for 15 to 21 days. The current CDC schedules (Table 8) can be followed but are unproved. I prefer an alternative regimen, also unproved (Table 9). Measuring trough penicillin levels in the CSF may be prudent. Close clinical and serologic surveillance following therapy is mandatory.
- Neurosyphilis with concurrent HIV infection poses a theoretical risk of aggressive and elusive spirochetal disease. The weight of evidence does not justify changes in current diagnostic and treatment recommendations for this patient population. Ongoing studies should provide definitive guidelines.

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Nifedipine

THERE ARE NOW a growing number of relatively isolated reports in small series of patients who get into great trouble using nifedipine sublingually or even orally, in so-called hypertensive crisis. These reports appear to cluster among persons who have been vasodepleted before, in terms of diuretic pretreatment. The patients are often old and frail. So, no different than with any other drug where you should be a little extra cautious in that group: giving a very potent, profound vasodilator, you want to be cautious. The dangers are the obvious ones—you drop the blood pressure too far too fast, and critical organs will not be perfused, especially the brain and heart.

Frankly, given this danger, what I now am urging patients to do is to bite the capsule a little bit, just get a small amount of the fluid, then take it out. Take it out of their mouth; hold it in their hand. Watch for a few minutes to see what the effect is and then, if necessary, take more. I don't give them the full dose unless I really need them to have an effect within minutes; then I might have them swallow the capsule. There's no reason, once you get some effect, to insist on getting the full effect. And as we know, in general, for these crises, you only want to drop the blood pressure maybe 10% or 20% over the first hour. You don't want to drop it to normal.

—PETER RUDD, MD

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Specialty Conference

Complications of Gastroesophageal Reflux

Moderator and Discussant
PAUL H. WARD, MD

Discussants
ANDREW F. IPPOLITI, MD; DANIEL H. SIMMONS, MD, PhD; *and* JAMES V. MALONEY, Jr, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Professor of Medicine.

Several specialists have recently recognized that gastrointestinal reflux causes complications resulting in significant disease. It causes discomfort, indigestion, esophagitis, Barrett's esophagus, and carcinoma of the esophagus. Pediatricians attribute many early pulmonary problems, and even some sudden deaths in infants, to the reflux of gastric contents. Otolaryngologists now recognize that many cases of nonbacterial, nonspecific pharyngitis and laryngitis are due to the reflux of gastrc acid secretions. Contact granuloma and cancer of the larynx may, in some instances, be secondary to nocturnal reflux. Thoracic surgeons and pulmonologists believe chronic tracheobronchitis and some cases of pulmonary disease are attributable to recurrent bathing of the respiratory epithelium by aspirated gastric contents. An awareness of the many complications of gastrointestinal reflux should lead to a multidisciplined attack on the factors responsible for these diseases.

(Ward PH, Ippoliti AF, Simmons DH, et al: Complications of gastroesophageal reflux [Specialty Conference]. West J Med 1988 Jul; 149:58-65)

PAUL H. WARD, MD*: Patients with chronic pharyngitis and laryngitis whose throat cultures do not show pathogenic organisms and who fail to respond to empirical trial courses of antibiotics have been a nemesis for physicians for years. Specific and less common granulomatous inflammatory diseases of the pharynx and larynx, such as sarcoid, syphilis, fungi, and tuberculosis due to bacterial organisms, are diagnosed by biopsy cultures.

Extensive studies of serial 16-mm motion pictures or videotapes[1] have recently been done of the pharynges and larynges of patients with chronic symptoms of pharyngitis and laryngitis. These patients complained of chronic sore throat, nonproductive cough, hoarseness, a choking sensation, laryngospasm, general discomfort, sticking sensations, dull pains, and a lump in the throat—signs and symptoms most likely due to gastroesophageal reflux.

Examination of the pharynges and larynges may show few or no objective physical abnormalities. In some patients, changes vary from a dull grayish loss of the glistening appearance of the mucosa to a heaped-up reddish granularity of the lymphoid follicles of the posterior pharyngeal wall and redness and edema of the vocal cords. In longer-term cases, there may be hyperkeratosis of the posterior commissure and granulomata on the arytenoids. Investigators previously recognized the predominant involvement of the posterior third of the larynx in these chronic and intractable cases of nonspecific laryngitis.[2-10] Many of the signs and symptoms may be caused by the stomach's acid contents refluxing to bathe the pharynx and posterior larynx secondary to the gastroesophageal reflux. Reflux occurs particularly at night when a patient is in a horizontal position. Because most people sleep either supine or on their sides, the posterior hypopharynx and posterior larynx are especially vulnerable to the regurgitated acid content. This acid produces the chronic irritation to the pharynx and larynx responsible for many cases of chronic nonspecific laryngitis and pharyngitis.

There is a paucity of experimental studies proving the relationship of the signs and symptoms to gastroesophageal reflux. The proof rests in careful history taking and in the therapeutic response, usually reported anecdotally. The commonly accepted symptoms and signs of gastroesophageal reflux are heartburn, esophagitis, regurgitation, upset stomach, belching with acid taste, epigastric and substernal pain, and nausea. In taking the history, it is important to ask patients if they feel something in their throat; experience fluid rush into the mouth while lying down, causing sudden coughing, throat clearing, and laryngospasm; have a history of healed ulcers; have had a previous gastric operation; have heartburn or ulcers; and use over-the-counter antacids.

We have presented cinematographic evidence to support the proposal that gastroesophageal reflux contributes to the pathophysiology of contact granuloma.[11] Studies of many cases strongly support the concept that the pharynx and larynx are irritated by refluxed stomach contents. The irritation produces a continual sensation of something in the throat initiating a desire to cough or clear the throat. Persistent and

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repetitive clearing of the throat results in violent approximation of the arytenoids, as was shown by Von Leden and Moore.[12,13] We are convinced that the continual irritation of repetitive coughing and clearing of the throat, resulting in a "kissing ulcer formation," and the presence of bacteria in the oropharynx cause the formation of the contact granulomas (Figure 1).

This study was stimulated by my personal experiences with a hiatal hernia, and I have on numerous occasions had the symptoms of peptic esophagitis and gastroesophageal reflux at night. Eating seafood or spicy foods or drinking wine or other alcoholic beverages, particularly when retiring soon thereafter, sets the scene for reflux regurgitation of gastric contents up into the pharynx. The reflux results in a sudden awakening with the presence of a sour acid taste in the mouth, coughing, laryngospasm, a need to sit upright, and an immediate attempt to harshly clear the throat. The next morning, there is often the sensation of something in the throat and the desire to repeatedly clear the throat and cough. During the clinical management of patients with chronic laryngitis, these patients habitually cleared their throats while being examined. This led to the practice of taking a cineesophagogram after the patient ingests barium of both thick and thin consistency and placing the patient in the Trendelenburg position after the barium was swallowed. A gastroesophageal reflux is frequently present.

Patients and Methods

During the past 12 years, we have photographed or videotaped the larynx and pharynx of more than 3,600 patients with laryngeal abnormalities; 138 of these were classified as chronic nonspecific pharyngitis and laryngitis, and 61 also had contact ulcers and granulomas. Serial 16-mm motion picture films or, more recently, ¾-inch videotapes were taken with the Berci-Ward telescope (Karl Storz Endoscopy of America, Los Angeles). The patients' charts, cineesophagograms, films, and videotapes were studied. This information has provided us with some interesting insights into the perplexing problem of chronic nonspecific laryngitis and pharyngitis, which have led to a more rational and highly successful approach to treatment. The presenting complaints vary widely and include hoarseness, a choking or sticking sensation, pain and chronic sore throat. The spectrum of pathophysiologic changes is broad, and the lesions tend to blend into each other.

Figure 1.—The photograph shows the larynx of a patient with reflux laryngitis. There is hypertrophy of the posterior commissure (top of picture) and a contact granuloma on the left vocal cord (**arrow**).

Cineesophagograms with Trendelenburg positioning were done in all cases. Reflux of the barium into the esophagus by stressing the patient during the cineesophagogram confirms the diagnosis and in some patients may reproduce some of their symptoms. Although hiatal hernias occur in an estimated 20% to 25% of the normal population, they were present in 80% of patients with nonspecific chronic laryngitis. A normal cineesophagogram does not rule out gastroesophageal reflux for it also occurs in so-called normal persons. Some of our patients with normal cineesophagograms gave strong histories of reflux with regurgitation and the tasting of acid contents. Other patients with chronic laryngitis said they did not have symptoms of reflux at night yet had hiatal hernias with easily demonstrable reflux on cineesophagograms. The confirmatory evidence that chronic laryngitis and pharyngitis, pachydermia, hypertrophic laryngitis, and contact ulcers and granulomas are due to chronic irritation from gastroesophageal-pharyngeal reflux rests heavily on the successful therapeutic responses in these patients.

Success in healing chronic nonspecific pharyngitis and laryngitis, contact ulcers, and granulomas by treating the patients for hiatal hernia and gastroesophageal reflux suggests that the latter mechanism may play an important part in initiating and perpetuating these problems. Whether the chicken (the irritation from gastric secretions) or the egg (the trauma of coughing and throat clearing) comes first is irrelevant. The important factor is that the vicious cycle of irritation, trauma, and more irritation can be broken in these cases by decreasing the irritation.

Treatment is simple yet difficult for many patients because it requires a change in life-style. The main meal should be eaten at noon, and the evening meal should be light and ingested at least four to five hours before going to bed. Fluids should be taken freely during the day and limited after the evening meal. Spicy foods, alcohol, and smoking should be avoided because they increase acid secretion. Overweight patients should lose weight. Antacids should be taken between meals and at bedtime. The head of the bed should be elevated from 15 to 25 cm (6 to 10 in) with bed blocks or bricks. If this is not practical, two to three pillows should be used to elevate the head and upper body. If the patient does not respond to this therapy, then histamine (H_2) receptor antagonists—such as cimetidine (Tagamet; Smith, Kline & French) or ranitidine (Zantac; Glaxo)—which inhibit the secretion of hydrochloric acid, are administered in therapeutic dosages.

In compliant patients (around 80%), the response has been dramatic with resolution of their symptoms and a return of the larynx and pharynx's physical appearance to normal. In nonresponsive and noncompliant patients with granulomatous lesions, biopsy studies are mandatory after three to

four weeks to rule out carcinoma. The possibility of chronic nonspecific laryngitis and pharyngitis predisposing to cancer has been addressed by several authors.[14,15] Gastroesophageal reflux is considered to have a carcinogenic effect in the case of Barrett's esophagus and carcinoma of the lower esophagus and stomach.[16,17] The development of a carcinoma in chronically nonhealed wounds, as well as in burn scars (Marjolin's ulcer), is usually recognized.

A series of carcinoma cases involving the larynx and pharynx in nonsmokers with gastroesophageal reflux is being accumulated, which strongly suggests that gastroesophageal reflux may be a predisposing factor in the development of carcinoma in these areas.

Finally, patients with stents and molds in their larynges and with prolonged maintenance of nasogastric feeding tubes should be considered possible candidates for gastroesophageal reflux and treated with antireflux measures to avoid the complications herein described.

Pathogenesis of Gastroesophageal Reflux Disease

ANDREW IPPOLITI, MD*: The precise cause of gastroesophageal reflux disease is not known. The condition does not have a single diagnostic criterion, such as an ulcer crater. Symptoms vary from the classic ones of heartburn and regurgitation to the unusual nonesophageal ones of coughing, wheezing, and throat complaints. Signs of inflammation may be absent or severe, such as esophageal ulceration or stricture. Given the wide range of manifestations of this disorder, it is difficult to identify any universal abnormal defects. The abnormalities that have been described result in a greater degree of exposure of the esophageal mucosa to acid and pepsin. They can be subdivided into those that increase the frequency of reflux and those that lengthen the duration of the reflux episodes (Table 1). Acid reflux can occur in healthy asymptomatic persons, but the frequency and duration of reflux is much greater in patients with esophagitis.

In healthy persons, acid reflux usually occurs after meals and is rare during sleep.[18] The lower esophageal sphincter is a barrier to acid reflux. While the sphincter is contracted, reflux rarely occurs and the sphincter is an adequate barrier over a wide range of resting pressures down to about 5 mm of mercury.[18] Reflux can develop, however, whenever the sphincter is relaxed, as happens during swallowing. Transient sphincter relaxation unaccompanied by swallowing is also recorded in healthy persons and can be associated with reflux. Reflux episodes are normally promptly terminated by peristaltic esophageal body contractions that empty the esophagus.

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TABLE 1.—*Pathogenesis of Gastroesophageal Reflux*

- Increased frequency of reflux
  - Lower esophageal sphincter incompetence
  - Delayed gastric emptying
  - Hiatal hernia
- Increased duration of reflux
  - Defects of esophageal peristalsis
  - Inadequate salivary secretion
- Potential mucosal irritants
  - Acid and pepsin
  - Bile and pancreatic enzymes
  - Drugs

Abnormalities That Increase the Frequency of Reflux

Incompetent Lower Esophageal Sphincter

In health, the sphincter is an adequate barrier to reflux, but abnormalities of sphincter competence are common in patients with esophagitis. They have an increased frequency of spontaneous relaxations and more relaxations associated with reflux. The explanation for these findings is not known. In addition, the resting tone of the sphincter may be so low—less than 5 mm of mercury—that it no longer acts as a barrier. Although this was once thought to be the primary defect in reflux disease, it is now apparent that a sphincter pressure below the normal range is still adequate to prevent reflux. Only at extremely low pressures is the sphincter incompetent. Finally, reflux can result when intragastric pressure exceeds the sphincteric pressure. In a series of patients with esophagitis, two-thirds of the reflux episodes were associated with transient lower esophageal sphincter relaxation. The other third was equally divided between transient increases in intra-abdominal pressure and spontaneous free reflux where the sphincter pressure was negligible.[19]

Delayed gastric emptying of food may contribute to an increased frequency of reflux in the postprandial period. About 40% of patients with reflux symptoms empty a radiolabeled meal significantly slower than healthy subjects.[20] The mechanism for this gastric defect is unknown.

Hiatal hernia is frequently associated with reflux disease; it is only an association, however, not causation. Most patients with hernia do not have frequent reflux symptoms, and some patients with symptoms do not have a demonstrable hernia. Nonetheless, hernias may contribute to an increased frequency of reflux during periods of increased intra-abdominal pressure. The anatomic location of the lower sphincter is normally below the diaphragm. Maneuvers that increase intra-abdominal pressure constrict the lower sphincter and thus help prevent reflux. In patients with hernia, the sphincter is above the diaphram and may not constrict as well when the intra-abdominal pressure is increased.

Abnormalities That Increase the Duration of Reflux

Defects of Esophageal Peristalsis

An important component of acid clearance from the esophagus is peristalsis. Both primary, swallow-induced and secondary peristaltic contractions follow acid reflux. In a recent series of patients, failed primary peristalsis was significantly increased in patients with esophagitis.[21] This refers to the failure of a swallow to elicit a peristaltic series of contractions throughout the esophagus. Consequently, the duration of the reflux episode is lengthened. Whether this causes esophagitis or is a result of esophagitis is unclear. This abnormality is uncommon in patients with reflux symptoms but without esophagitis.

Defective Salivary Secretion

In a supine healthy subject, about four minutes are required to clear a bolus of acid from the esophagus when dry swallows are taken every 30 seconds. When saliva was aspirated from the subjects with a mouth cannula, however, the clearance time of the acid was prolonged fourfold.[22] Acid

clearance may thus require neutralization by salivary secretions.

The noxious refluxed material usually includes acid and pepsin, but experimental evidence indicates that trypsin and bile acids are also injurious to the esophagus.[23] They have the major role in the reflux esophagitis seen in patients after antrectomy and may also play a role in patients with an intact gastrointestinal tract.[24] Finally, various medications are potentially injurious to the esophagus and may contribute to the development of esophagitis. These include antibiotics, especially doxycycline, potassium chloride, ferrous sulfate, aspirin, nonsteroidal anti-inflammatory drugs, and quinidine.[25]

Diagnosing Gastroesophageal Reflux

The diagnosis of gastroesophageal reflux is easily and accurately based on the classic symptoms of heartburn and regurgitation. In patients with pulmonary or pharyngeal complaints, however, diagnostic tests are needed to determine the presence and severity of reflux disease and its correlation with other complaints.

Although an upper gastrointestinal series is helpful in excluding other diseases and complications of esophagitis, such as a stricture, it is not useful in assessing the presence or severity of reflux. A hiatal hernia is too common a finding to be specific for reflux, and spontaneous reflux of barium from stomach to esophagus occurs infrequently in patients. Esophageal motor abnormalities, reduced sphincter pressure, and esophageal body contraction amplitude and failed peristalsis are not specific for reflux but, when present in a patient with known reflux, do reflect severity. The Bernstein test, on the other hand, does indicate the symptomatic sensitivity of the esophageal mucosa to acid. The test is positive in about 80% of patients with reflux symptoms.[26] Its limitations are that the test is not a gauge of severity and it is not known whether patients with unusual manifestations of reflux, such as coughing, wheezing, or throat pain, are Bernstein positive.

The endoscopic finding of an erosive, exudative esophagitis is highly specific for the existence of severe reflux disease. Questionable lesions can be further assessed by biopsy specimens confirming an acute inflammatory infiltrate and microulceration. Lesser degrees of inflammation, such as hyperemia and friability of the mucosa, are more subjective and less certain. The prevalence of esophagitis is dependent on the population studied, and its frequency in patients with pulmonary or pharyngeal disease has not been established.

The most promising test to determine the presence and severity of reflux and its relationship to nonesophageal symptoms is 24-hour pH monitoring. A small pH electrode can be placed to a Holter-type monitoring device to obtain an outpatient study. The study can be done in a patient's natural environment rather than in hospital. Acid reflux frequency and duration are recorded and the total time of esophageal acid exposure calculated. In addition, by means of a diary, the association between symptoms and reflux can be ascertained. Studies have shown an approximately 90% sensitivity and specificity for prolonged esophageal monitoring.[26] It has not been used in patients with pulmonary or pharyngeal disease, however.

Treating Gastroesophageal Reflux

The treatment of gastroesophageal reflux has been extensively reviewed.[26,27] The three modalities of therapy are supportive measures, antisecretory drugs, and smooth muscle stimulants. In the final analysis, the association of reflux disease and nonesophageal lesions will rest on ameliorating those lesions with antireflux therapy.

The principal supportive measures are elevating the head of the bed, abstaining from food before bedtime, avoiding tight clothing, and taking antacids. Clinical trials have not established the efficacy of antacids as compared with placebo either in relieving symptoms or healing esophagitis. But their use has become common practice, especially on an as-needed basis.

The H_2 receptor antagonists, cimetidine, ranitidine, and probably famotidine, are the mainstays in the treatment of reflux. The longer duration of action as compared with antacids makes them especially useful in the control of nocturnal reflux. The efficacy of cimetidine and ranitidine in controlled clinical trials has been established.[27,28]

The smooth muscle stimulants, bethanechol chloride and metoclopramide hydrochloride, potentially increase sphincter pressure and the amplitude of esophageal body contractions. Their efficacy in reflux, however, may depend on nonesophageal effects such as the stimulation of salivary output for bethanechol and an acceleration of gastric emptying for metoclopramide.[22,29] The combination of metoclopramide and cimetidine has been useful for refractory patients.[30]

Barrett's Esophagus

Barrett's esophagus is an increasingly important complication of reflux disease. It is defined as the replacement of the squamous mucosa of the esophagus by columnar epithelium. The finding of specialized epithelium of the intestinal type establishes the diagnosis of Barrett's, which is a severe form of reflux disease, and its prevalence reflects that fact. It is found in 12% of patients with reflux symptoms but in a third of patients with esophagitis and in nearly half of patients with a benign stricture.[31] It is predominantly a lesion in white men and can be found in children as well as in adults. Its clinical importance lies in its association with adenocarcinoma of the esophagus. At present, adenocarcinoma in cases of Barrett's esophagus accounts for a third of all esophageal cancers. The prevalence of adenocarcinoma at the time of the diagnosis of Barrett's esophagus is 10% on average.[31] Although patients with known Barrett's esophagus are surveyed to detect cancer, the efficacy of this search has not yet been established. Dysplasia is a frequent accompaniment of adenocarcinoma in patients with Barrett's esophagus, and the detection of dysplasia at a precancerous state is important. Unfortunately, a third of patients with adenocarcinoma in a Barrett's esophagus have no antecedent history of reflux.

Pulmonary Problems Due to Gastroesophageal Reflux

DANIEL H. SIMMONS, MD, PhD*: In this section I will consider some specific questions about the relation between pulmonary problems and gastroesophageal reflux in adults. Most of the questions do not have clear-cut answers because there are little well-controlled quantitative data and because the clinical conditions are not well defined. First, criteria for gastroesophageal reflux adequate to cause pulmonary symptoms are not clear. For example, it is not known if it must be severe

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enough to cause erosive esophagitis or be associated with other abnormalities, such as pharyngeal or cricothyroid muscle dysfunction.[32] Second, criteria for defining associated pulmonary problems vary considerably. To illustrate, the disease asthma is often not distinguished from the symptom wheezing and pulmonary fibrosis is not classified by the usual radiologic criteria. But patching together numerous reports still gives some useful information on the subject.

First, is there an association between reflux and pulmonary symptoms or disease and, if so, is it cause-and-effect? Three large studies report that half to two thirds of selected patients with asthma[32-34] have gastroesophageal reflux compared with 5% to 17% of control subjects; conversely, 3% to 46% of patients with gastroesophageal reflux have asthma.[32] It is also reported in about half the cases of pulmonary fibrosis[35]—although others question whether these are of true diffuse fibrosis[33]—and 4% of patients with gastroesophageal reflux are said to have pulmonary fibrosis. These rates are so much greater than for the general population[35] that cause-and-effect seems likely even though definitions of significant reflux and respiratory problems are not clear-cut. Second, the association is also suggested by the correlation between the amount of reflux and the severity of pulmonary symptoms both before and during sleep and before and after medical[36] or surgical[37] treatment of gastroesophageal reflux. Third, in one series tracheitis from aspiration preceded asthma by 3 to 17 years in half the cases.[37] Finally, infusing acid into the esophagus while preventing aspiration causes asthmatic symptoms in humans and reflex bronchospasm in animals, clearly cause-and-effect.[36]

A cause-and-effect relation between gastroesophageal reflux and pulmonary problems is far from absolute. Reflux confirmed by esophageal pH measurements often does not elicit symptoms in patients with pulmonary disease, and complete surgical correction of gastroesophageal reflux improves preexisting asthma only about half the time.[37]

Second, what pulmonary symptoms or disease are associated with gastroesophageal reflux? So far, only asthma and fibrosis have been discussed here. Many other respiratory consequences of gastroesophageal reflux have been mentioned, however, including chronic bronchitis even in nonsmokers; chronic pulmonary insufficiency of unknown pathogenesis or incidence[38]; recurrent bronchopneumonia; atelectasis; hemoptysis; and sleep apnea and its consequences, definitely present in infants and possibly present in adults. Lower lobe fibrosis and volume loss from chronic aspiration may be a common result of reflux, although there are no data on its incidence.

Third, what is the mechanism of the cause-and-effect relation? The association between gastroesophageal reflux and pulmonary problems was long thought to be due to gastric acid aspiration into the lungs after reflux into the esophagus; this is not always the case. Although hydrochloric acid is usually assumed to be—and likely is—the main offender, food particles and other material small enough to reach distal airways may cause another type of inflammation and pulmonary problems. Also, there is the previously mentioned vagal reflex bronchospasm when acid reaches the esophagus without reaching the trachea.[39] This reflex, however, may not be clinically important since acid in the airway of animals causes much more bronchospasm than the reflux does.

Gastroesophageal reflux is usually assumed to be the cause and pulmonary problems the effect when they occur together. In fact, cause and effect may be reversed; a drop in the esophageal pH due to gastroesophageal reflux can follow respiratory symptoms rather than precede them,[39] usually from increased abdominal pressure during cough or decreased intrathoracic pressure during inspiration.

The next question is whether gastroesophageal reflux merely exacerbates preexisting pulmonary disease or whether it can cause disease de novo. Flare-ups of asthma are often ascribed to gastroesophageal reflux, but reflux is not often thought of as the cause of an asthmalike syndrome from repeated acid insults leading to inflammation and nonspecific hyperreactivity of the airways. It has also been suggested that acid aspiration may be one little-recognized cause of diffuse idiopathic pulmonary fibrosis,[35] although the laboratory criteria for this suggestion are probably no longer valid. Rather, it seems likely that many cases of fibrosis differing radiologically from idiopathic fibrosis are in fact due to recurrent small and frequently unrecognized acid aspirations—particularly during sleep when physiologic conditions predispose to aspiration.

An example of gastroesophageal reflux causing "asthma" is the case of a 68-year-old woman seen at UCLA. She had never smoked nor had any respiratory complaints until three years previously, when she began to have about two episodes of severe bronchitis with productive cough each year. One year before being seen, continuous and disabling wheezing developed. This was thought to be asthma, and bronchodilator and steroid therapy was started without relief. Her x-ray film showed some linear atelectasis at one base. At UCLA, she gave a history strongly suggesting long-standing gastroesophageal reflux that had never been treated adequately. Auscultation of the lungs revealed large airway sounds more consistent with severe inflammation than with asthmatic bronchospasm. Endoscopy then showed erosive esophagitis, confirming severe gastroesophageal reflux. Her bronchodilator regimen was stopped abruptly, her prednisone dose was tapered off, and a strict medical regimen for reflux started. Two months later, her wheezing had cleared almost completely and repeat endoscopy was normal. Her "asthma" was ascribed to chronic gastric acid aspiration. Although gastroesophageal reflux therapy may have been mainly responsible for the patient's improvement, discontinuing her pulmonary medications may also have helped, because they can increase gastroesophageal reflux. Finally, decreasing her airways obstruction may have decreased her gastroesophageal reflux.

The next question: If a patient has pulmonary symptoms or disease, what are the indications for evaluating the possibility of gastroesophageal reflux? Unfortunately, proposed criteria for starting a workup are untested, and a clinician must decide by the number and importance of findings suggestive of reflux. The following independent sets of criteria have either been suggested or seem appropriate.

- The presence of any chronic pulmonary symptoms or disease,[38] with or without symptoms of gastroesophageal reflux. This is the most liberal criterion proposed, and is based on the high incidence of gastroesophageal reflux in asthma and pulmonary fibrosis.
- Symptoms suggestive of reflux in any patient with a chronic pulmonary problem.
- The onset of "asthma" in a nonatopic, nonsmoking adult, as in the case presented.[40]

• Resistance of asthma to conventional therapy, including steroids. Worsening of symptoms during therapy is an even stronger criterion because pharmacologic treatment can increase reflux.

• Unexplained persistent worsening of asthma.

• Nocturnal appearance or exacerbation of pulmonary symptoms, such as cough, wheezing or asthma, shortness of breath, or morning hoarseness. Although many persons with asthma who do not have gastroesophageal reflux are worse at night, these symptoms are more common in asthmatic patients with proven gastroesophageal reflux than without it and therefore may be due to gastroesophageal reflux.

• The presence of bilateral basal rales coarser than those of diffuse idiopathic interstitial fibrosis in the absence of congestive heart failure. In one study, rales were present in almost all patients with fibrosis associated with gastroesophageal reflux.[35] This finding could be one of the simplest and most useful criteria for suspecting a chronic pulmonary problem due to reflux.

• Chest x-ray abnormalities, including

Bilateral chronic basilar infiltrates or volume loss or both. In one series, this was found in almost all patients with fibrosis associated with gastroesophageal reflux.[35]

Recurrent transient infiltrates suggestive of acute aspirations, most often in the lower lobes, but not exclusively so.

Diffuse fibrosis. This is usually patchy rather than uniform as in idiopathic pulmonary fibrosis.

The next question: how should coexisting gastroesophageal reflux and pulmonary problems be treated? First, as many as 50% of patients with asthma have less wheezing and improved flow rates following adequate medical therapy for gastroesophageal reflux alone.[34,36,39,40] After successful surgical correction of gastroesophageal reflux, significant improvement has been reported in 50% and 65% of cases in two series, although asthma may occasionally get worse after the operation. These data suggest that it is appropriate to put all patients with coexisting significant pulmonary symptoms and gastroesophageal reflux on optimal medical therapy and even to consider surgical intervention. Medical therapy may also be used diagnostically; a decrease in pulmonary symptoms suggests a cause-and-effect relation to gastroesophageal reflux.

A second therapeutic maneuver is optimizing bronchodilator and steroid therapy. Using bronchodilators increases gastroesophageal reflux by relaxing the lower esophageal sphincter and decreasing lower esophageal pressure. Theophylline use also stimulates gastric acid production. Steroids are no longer thought to increase acid secretion; unfortunately, neither do they block inflammation from either acute or chronic aspiration. When reflux is the sole cause of the respiratory problem, the use of all these medications should be stopped.

Antibiotics are generally not indicated in cases of chronic aspiration from gastroesophageal reflux since it rarely leads to bacterial infection. Major acute aspirations cause infection about 60% of the time, so antibiotics may occasionally be useful in patients with gastroesophageal reflux. Taking antitussives may relieve troublesome cough, but this symptom causes reflux in only about a third of patients with chronic gastroesophageal reflux.

In summary, the following seem likely:

• There is a very common association between gastroesophageal reflux and pulmonary problems, which are usually exacerbations of preexisting disease;

• Roughly half the time the association is cause-and-effect;

• Reflux is usually the cause rather than the effect, but the opposite can be true;

• Preexisting asthma appears to be the disease most often affected by gastroesophageal reflux;

• Diseases caused by gastroesophageal reflux include airways obstruction simulating asthma and fibrosis;

• Reasonable criteria are available for investigating a possible relation between pulmonary problems and gastroesophageal reflux in specific situations;

• The most important treatment of reflux-related problems is conventional treatment of reflux itself;

• When airway disease is caused by gastroesophageal reflux, drug therapy for lung disease should be discontinued because it increases gastroesophageal reflux.

The Reflux-Aspiration Syndrome

Surgical Considerations

JAMES V. MALONEY, JR, MD*: Treatment of the reflux-aspiration syndrome by a surgical procedure is not difficult, and the results are remarkably good. The challenge lies in recognizing the syndrome and differentiating it from other disorders that may cause similar symptoms. The diagnostic problem is illustrated by the following three cases:

Patient 1. A 41-year-old film executive had spells of unconsciousness on eight occasions in three weeks. Three weeks before being seen, the patient had paroxysms of coughing at a time when an upper respiratory tract infection produced similar symptoms in two other members of the family. One paroxysm occurred when the patient was walking alone on the street at night and terminated in a period of unconsciousness and mild injury. Repeated similar spells of unconsciousness were associated with some of the paroxysms, three of these occurring during the night. He was seen in consultation by his personal physician, a pulmonary medicine specialist, and an otolaryngologist. It was concluded that his cough was causing unconsciousness by impairing venous return to the heart. The terrified patient was afraid to sleep, walk, or drive an automobile.

Patient 2. A 66-year-old metal broker was seen because of cough. He began having dry cough at age 60. For the next three years, the nonproductive cough progressed in severity. Pulmonary function tests were negative, and bronchoscopy was normal. There was a progressive increase in the production of thick yellow sputum to ¾ cup per day (200 sheets of facial tissue). A trial of antibiotic therapy had no effect. The cough was so incessant and so severe that the patient had to watch television in a separate room from his wife and sleep in a separate bedroom. He awakened each night at 11 PM with severe paroxysms of coughing. He spent most of his sleepless nights sitting up coughing and was too fatigued to work effectively during the day. Sleep deprivation and chronic fatigue resulted in a weight loss of 9 kg (20 lb).

Patient 3. A 67-year-old physician was thought to have lung cancer. On a routine chest film taken two weeks previously, a 2-cm lesion, not present six months previously, was noted in the left upper lobe. He was a 30-pack-year smoker

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who had stopped smoking at age 37. Tomograms, computed tomographic (CT) scans, and sputum cytology done under the direction of several physicians showed no evidence of malignant disease. A review of systems was noncontributory except for a 30-year history of repeated episodes of tracheitis, intermittent raspy voice, and episodic nocturnal asthma for which he took oral theophylline and ephedrine.

These three patients share in common a diagnosis of regurgitation and aspiration as the explanation for their symptoms and findings, consultation with a number of specialist physicians over a period of years without a diagnosis having been made, and invasive physiologic studies—esophagoscopy, manometry, bronchoscopy, and continuous pH recording—that failed to identify the problem.

The runaway costs of health care are, in considerable measure, related to the creation of diagnostic tests that are expensive, frequently hazardous, and that have a sensitivity, specificity, and accuracy that are so low that they are of limited value in the decision-making process. Nevertheless, the use of such tests is occasionally justified because, even when negative, they rule out alternative diagnoses as a cause of a patient's symptoms. Such is the case in these three patients in whom such conditions as Zenker's diverticulum, dysfunction of the superior laryngeal nerves, diffuse esophageal spasm, and other conditions were ruled out by the negative tests.

If modern technology cannot provide a definitive diagnosis of reflux aspiration, how, then, does one diagnose the syndrome? The best method is that which we have recommended for generations to second-year medical students who are being introduced to the methodologies of clinical medicine: Take a careful history and be familiar with the classic description of disease syndromes. To illustrate the preeminent importance of a careful history, it is worth reviewing the subtleties that were noted during the history taking and that permitted a definitive diagnosis at the time of the initial surgical workup of the three patients.

Patient 1 (unconscious spells):

- Paroxysms: "Can cough but can't breathe in"—typical of adductor spasm of the vocal cords due to stimulation of the superior laryngeal sensory nerves by gastric contents.
- "Crowing noise" with cough—adductor spasm.
- "'Rice Crispies' sounds in the right lung, but never in the left"—Bronchial adventitious sounds associated with endobronchial foreign material. Aspiration is twice as likely in the right lung as in the left. On which side does the patient sleep at night?
- Nap after lunch causes severe coughing—recumbency with a full stomach causes aspiration.
- Indigestion: Although the patient said he did not have indigestion at present, ten years ago he suffered pyrosis and dysphagia, for which he took antacids.
- Obesity: He noted ten years ago that when his weight was 100 kg (220 lb), his peptic acid symptoms were severe and that at 90 kg (198 lb), his symptoms were mild. (Obesity greatly increases the problem of reflux due to increased intra-abdominal pressure.)
- Nocturnal regurgitation: Awakens with a sour taste in the mouth. (Patients who reflux often do not mention this unless specifically questioned.)
- Raspy voice that comes and goes; watery eyes—chemical laryngitis.

A brief period of intensive medical therapy reduced the patient's symptoms and eliminated the unconscious spells. An operation relieved all symptoms. The chemical laryngitis required four months to resolve.

Patient 2 (persistent productive cough):

- Orange juice causes instantaneous cough. (Orange juice may sometimes produce ulcer pain in 10 to 15 minutes. The acidic pH causes a discomfort in the presence of peptic esophagitis immediately after deglutition.) An instantaneous cough means that the stimulus arises in the pharynx and larynx, suggesting chemical laryngitis.
- Episodic pneumonia: The patient said he had never had pneumonia, but old x-ray films showed at least two episodes of transient aspiration pneumonia during the previous decade.
- Bronchoscopy done several years previously was followed by a severe episode of pneumonia requiring a week in hospital—topical anesthesia of the airway used for bronchoscopy eliminated the natural defense mechanism against postoperative aspiration.
- Raspy voice and watery eyes: Although the patient did not complain about it, mild laryngitis was apparent during the course of the history taking and, when noted, the patient said it had been occurring intermittently for some years.
- Anosmia: The patient lost his sense of smell ten years previously—due to the injury of the olfactory membranes by the coughing of acidic gastric contents.
- Sour taste in mouth at night. (Nocturnal regurgitation is characteristic, and this patient said it related to the amount of food he ate and the time he ate before retiring.)
- Sleeps in recliner. (A principal complaint was loss of sleep due to cough, and careful questioning showed that he usually spent the night in a chair after waking up and coughing; the erect position reduces reflux.)
- Indigestion. Although the patient specifically said he did not have indigestion, he admitted that between ages 45 and 55, he drank 15 to 20 cups of coffee a day, suffered from pyrosis, and consumed 20 to 30 antacid tablets (Tums) per day.

A fundoplication cured the symptoms of regurgitation, and his sense of smell is gradually returning. Because the cough persisted, bronchography was done and showed extensive left lower lobe bronchiectasis. A segmental resection of the three basal segments of the left lower lobe was done. The cough immediately disappeared.

Patient 3 (physician with left upper lobe tumor):

- "Tracheitis" recurring over 30 years. The episodes occur as often as three to four times a year—due, of course, to aspiration.
- Aspiration: On a single occasion, after a large spaghetti dinner, the patient regurgitated and aspirated, resulting in roentgenographically proved pneumonia. (Such an episode would not occur in a conscious, normal person.)
- Asthmatic attacks, always nocturnal, occurring at intervals of from one to three months. He awakens in the night wheezing, sits up, takes oral theophylline and ephedrine, and then returns to sleep after an hour or two. (Aspiration while sleeping causes bronchospasm. The role of reflux aspiration in infantile asthma has been well documented.)
- Raspy voice, intermittent for several years, often associated with bronchitis—chemical laryngitis.

- Bronchoscopy done twice in 30 years was normal.
- Pulmonary lesion: A presumptive diagnosis of tumor was made on the basis of a 2-cm mass in the left upper lung field, proved by tomography and CT scan, and known not to have been present six months previously. At the time of the initial history, an ancillary diagnosis of the reflux-aspiration syndrome was made on the basis of the history and evidence of chronic basilar lung disease on the chest radiograph. The basilar lung disease was thought to be unrelated to the upper lung field lesion. Because of the evanescent nature of many pulmonary lesions, as a matter of personal policy, I never use surgical therapy for pulmonary lesions unless I have followed and documented the unchanging nature of the lesion over a period of three weeks. A surgical procedure was therefore scheduled three weeks in advance. A week later, the patient and his family requested an immediate operation because of the special concern that a physician has for the nature of pulmonary cancer. I refused to advance the operation date because the well-known increased complication rate associated with operations on physicians is due to making "exceptions" from what is presumably the optimum method used on other patients. When the patient was admitted for an operation three weeks after the initial visit, the pulmonary lesion had almost completely disappeared, indicating that it represented an area of pneumonia due to aspiration. The patient is currently under study for his reflux-aspiration syndrome.

Conclusion

Operative treatment may be overused in patients with symptomatic hiatus hernia and peptic esophagitis. A tenth of the population has in a lifetime one or more transient episodes of symptoms due to acid-peptic hypersecretion, and 25% of persons older than 50 years have a hiatus hernia. There are, therefore, millions of patients who have a concomitance of the two conditions. Many patients have operative procedures to restore the competence of the gastroesophageal sphincter during such a transient episode of peptic acid hypersecretion when, in fact, the presence of the hiatus hernia is not a physiologic problem. Medical therapy, particularly with an H_2 receptor antagonist, is the appropriate treatment for such patients.

In contrast, as these three cases show, patients with the reflux-aspiration syndrome may suffer progressive, incapacitating disease because the nature of their condition is unrecognized. The diagnosis is often missed because the symptoms, signs, and physiologic findings of peptic esophagitis are either absent or are not a prominent feature of the clinical history. It is not possible to estimate the incidence of pulmonary disease due to this syndrome. The frequency with which pathologists diagnose "lipoid pneumonia"—now recognized to be due to aspiration—at routine autopsy suggests that the incidence is far greater than is the clinical recognition of the syndrome. We should direct our best efforts to recognizing this syndrome and subjecting the patients, under appropriate circumstances, to operations that restore the competence of the gastroesophageal sphincter. The taking of a careful history is more valuable in identifying the reflux-aspiration syndrome than is any currently available diagnostic test.

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Medical Staff Conference

Stratifying Risk After a Myocardial Infarction

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *For patients surviving myocardial infarction, the most important concern is that of prognosis and of influence of therapy. Recent studies have shown that the risk of subsequent cardiac morbidity or mortality can be estimated by tests done in the postinfarction convalescent period. These tests define the populations in whom therapeutic interventions will be studied to determine the influence of therapy on long-term outcome. Dr. Nora Goldschlager, the Director of the Coronary Care Unit at San Francisco General Hospital and Medical Center, will discuss this important subject.*

NORA F. GOLDSCHLAGER, MD†: Survivors of myocardial infarction (MI) can be classified into three clinically definable groups with respect to their postinfarction course and prognosis: high risk, low risk, and moderate risk.[1-3] The characteristics of those at high risk for subsequent cardiac events (recurrent MI, death, recurrent angina requiring revascularization) are continuing myocardial ischemia (as determined by a predischarge exercise test), left ventricular dysfunction (usually assessed by radionuclide angiographic techniques), and complex ventricular extrasystolic activity (multiform complexes, bursts, or sustained ventricular tachycardia as shown by predischarge ambulatory electrocardiographic monitoring). This high-risk group has a mortality of 20% to 50% in the first year after an MI. Patients at low risk for cardiac events in the first one to two years following a myocardial infarction are those who have had their first infarction and who have no evidence of ongoing myocardial ischemia or complex ventricular extrasystolic activity at the time of hospital discharge. These patients have an annual mortality of only about 2% to 5%. The rest constitute a group at moderate risk and usually have one or more of the "risk" features; their mortality in the first postinfarction year is about 10%. In recent years, identification and characterization of these clinical groups have received a great deal of attention, with a view towards reducing morbidity and mortality after a myocardial infarction. This discussion will focus on the techniques for "stratifying risk" and the implications for management of a patient who has had an MI.

Exercise Testing

The purpose of doing a predischarge exercise test is to assess whether postinfarction myocardial ischemia is present.[4-8] The documentation of myocardial ischemia indicates that additional cardiac muscle is in jeopardy of being infarcted. Both treadmill and bicycle methods can be used; the treadmill is often preferred because walking is easier and less fatiguing than cycling. As the patient incrementally increases the workload, the supervising physician notes the occurrence of angina, breathlessness, pallor, diaphoresis, or unsteadiness of gait and changes in blood pressure or in the electrocardiographic record (ST segment changes or arrhythmias). Correlative data of this nature are not available from other techniques of evaluating patients who have had an MI. A 12-lead electrocardiogram (ECG) is recorded every 90 seconds during exercise and every minute in the recovery period; several ECG leads are used to enhance the sensitivity for detecting multivessel coronary artery disease documented by coronary angiography. A finding of anatomic multivessel disease, however, does not per se indicate either the amount or the location of specific areas of myocardium that are at "ischemic risk." Techniques such as thallium scintigraphy or radionuclide ventriculography are often used to make this assessment, thereby improving the predictive capability for future cardiac events.

The safety of exercise testing before hospital discharge is now established and relates in part to the careful selection of patients for the test. Depending on the particular hospital population, 40% to 75% of all patients who have had an MI can undergo exercise testing.[7,8] Common exclusion criteria are postinfarction anginal pain, systolic hypertension ($\geq$ 150 mm of mercury), congestive heart failure, atrial or ventricular arrhythmias recorded at rest, and an unstable resting ECG. Many patients having these conditions would benefit from prolonging their hospital stay to optimize their treatment regimens; exercise testing can be done when—and if—clinical stability is achieved. Resting sinus tachycardia, advanced age, a sedentary life-style, and concomitant disease may also constitute reasons for exclusion. The use of, or need for, cardioactive medications such as digitalis preparations, nitrates, diuretics, β- or calcium channel-blocking agents, and antiarrhythmic drugs does not constitute sufficient reason for exclusion from exercise testing, nor does a depressed ejection fraction per se. In view of these exclusion criteria, exercise testing is obviously done predominantly in patients who are in New York Heart Association Functional Class I or II at the time of hospital discharge, who are expected to do relatively well. Exclusion from exercise testing itself defines a group of patients at high risk for a future cardiac event. In one study, exclusion from exercise testing

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ABBREVIATIONS USED IN TEXT

ECG = electrocardiogram
ESV = end-systolic volume
MI = myocardial infarction

was the strongest single predictor of subsequent mortality,[2] correctly predicting 58% of nonsurvivors.

The two commonly used exercise test protocols are a heart rate-limited one (in which a patient's attaining a heart rate of 120 to 130 beats per minute serves as the criterion for stopping the test) and a symptom-limited one (in which the patient exercises to symptoms, or signs, that preclude further exercise).[8,9] The advantage of the symptom-limited test is the ability to obtain the greatest diagnostic yield from the test in terms of maximum achieved heart rate, the greatest magnitude of ST segment depression, and the highest frequency and complexity of ventricular ectopic activity. Limiting symptoms and signs are moderate to severe angina; dyspnea; lightheadedness; pronounced fatigue; three or more consecutive ectopic ventricular complexes; systolic hypertension (≥ 180 mm of mercury) and hypotension (a fall in systolic pressure of 10 mm of mercury or more), especially if it is accompanied by an abnormal ECG or anginal pain.[10] Significant ST segment depression—2 to 5 mm—occurring in the absence of symptoms or signs of ventricular dysfunction has served as an indication to terminate exercise in some, but not all, laboratories (Figure 1).[7-9] Using the aforementioned criteria for candidacy for exercise testing and for stopping exercise, complications such as extension of the myocardial infarction, unstable angina, or sustained ventricular tachycardia or ventricular fibrillation have not been reported.

Responses to predischarge exercise testing will reflect the particular population being studied, the test protocol used, and the use of cardioactive medications.[11] From 30% to 75% of patients are able to achieve a heart rate equal to 70% of their age-predicted maximum—patients taking β-blocking drugs usually cannot attain this heart rate—and 20% to 60% can perform a workload of 5 mets (1 met [metabolic equivalent] = a unit of basal oxygen consumption, or 3.5 ml O_2 per kg of body weight per minute). In symptom-limited tests, angina occurs in 6% to 15% of patients, hypotension in about 10%, and notable fatigue in about 30% to 50%. Breathlessness occurs in most—60% to 100%—patients.

Electrocardiographic abnormalities, specifically ST segment depression, occur in 25% to 30% of patients, most of whom do not experience anginal pain. In current practice, many physicians terminate exercise tests if substantial—3 to 5 mm—ST segment depression occurs. The prevalence and magnitude of ST depression will be increased by doing symptom-limited tests rather than heart rate- or workload-limited ones. Because both the presence and absence of ST segment depression have import for predicting the extent and severity of angiographically demonstrable coronary artery disease and for prognosis, an argument may be made for routinely doing symptom-limited tests.

Ventricular arrhythmias are noted in 20% to 60% of patients[4,11,12]; salvoes—three or more consecutive venticular extrasystoles—and multiform ventricular extrasystoles occur infrequently: 1% to 2% of patients. Neither sustained ventricular tachycardia nor ventricular fibrillation has been reported to date. The frequency of ventricular ectopic activity is similar in heart rate- and symptom-limited exercise tests,[9] suggesting that using the latter protocol does not reduce the safety of the test.

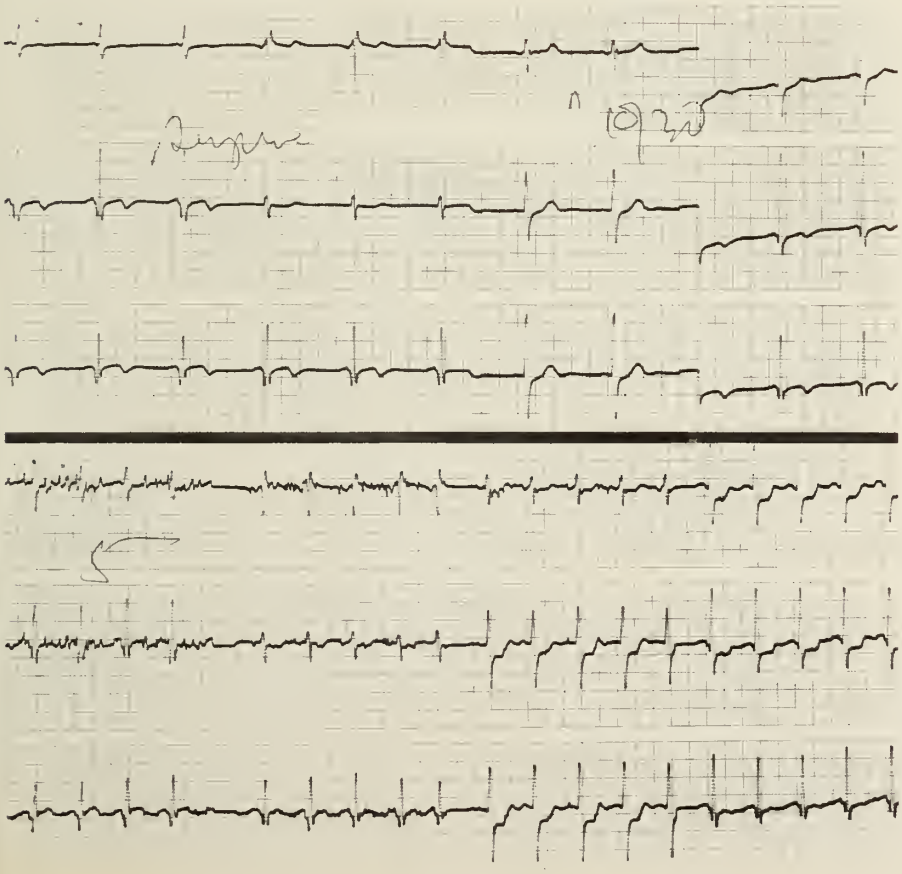

Figure 1.—Top, A resting 12-lead electrocardiogram was done in a 56-year-old man being discharged from the hospital after an uncomplicated inferoposterior wall myocardial infarction. Q waves are present in leads II, III, aV_F, and V_5 through V_6 and a prominent R wave is present in lead V_1. **Bottom,** After five minutes of treadmill exercise during which the patient had no symptoms, pronounced ST segment depression with horizontal configuration is seen in leads V_2 through V_5. Horizontal ST depression is also present in lead aV_L. These ST segment changes might represent anterior wall myocardial ischemia or a reciprocal change to inferoposterior wall infarction. The stress electrocardiogram does not distinguish the two possibilities.

Prognostic Value of the Exercise ECG Response

In assessing prognosis, a normal predischarge exercise test is as important as an abnormal one. In the original study of Théroux and colleagues,[7] 62% of 210 patients did not have ST segment depression, angina, hypotension, or significant ventricular arrhythmias. Of these patients, 54% had a benign course in the first year after an MI; stable angina developed in 35%, unstable angina in 3%, recurrent MI in 6%, and 3% died. Thus, serious postinfarction problems—death, recurrent MI, and unstable angina—developed in only 12% of patients. This low risk in patients with a "normal" exercise test after an MI has been confirmed by virtually all investigators,[6,8,11] despite the facts that patients are variably managed at the time of the exercise test and that the test results do not necessarily influence subsequent medical management. Especially noteworthy is the low—less than 5%—incidence of death of cardiac causes in the first postinfarction year.[6-8,13-15]

The prognostic value of exercise ST depression was recognized in the late 1970s; subsequently published studies have tended to confirm the initial observations. Théroux and colleagues found that ST depression developed in 30% of 210 patients[7]: 10% of the 210 died in an average one-year follow-up period; 85% of patients who died and 91% who died suddenly had had exercise ST depression. One-year mortality in patients with ST depression was 27%, in contrast to a 2% mortality in patients without ST depression. The occurrence of angina did not add to the prognostic value of ST depression alone—emphasizing the clinical importance of "silent" ischemia.

As major morbidity and mortality are not frequent in patients who have had an MI who qualify for predischarge exercise testing on the basis of their low risk, ST depression has a low overall predictive accuracy for these events. Nevertheless, patients with this abnormality warrant close follow-up. The issue of whether to treat such patients with nitrates or β- or calcium entry-blocking agents to prevent or reduce the ischemic ECG response is unresolved, and no standard management regimens are currently used. Similarly, the roles of early coronary angiography and myocardial revascularization in this patient group are just beginning to be defined.

It seems rational to attempt to refine exercise test responses to achieve a higher predictive accuracy than 30% for major cardiac events. To this end, nuclear imaging techniques have been used along with exercise electrocardiography to assess the relationship between ST segment deviation and amount and location of myocardium supplied by a stenosed coronary artery and therefore at risk for ischemia or infarction.

Ventricular Arrhythmias

The significance of exercise-induced ventricular arrhythmias in patients who have had an MI remains controversial. The reported incidence of any exercise ventricular arrhythmia ranges from 15% to 56%; many patients are already receiving antiarrhythmic (including β-blocking) medications, and others are placed on such therapy as a consequence of the exercise test results, thus potentially altering the clinical course. The highest reported incidence of exercise-related ventricular arrhythmias—56%—occurred in a series of asymptomatic patients who, receiving no medications at hospital discharge, represented a population free of complications.[11]

In contrast to ST segment depression, exercise-induced ventricular arrhythmias are not highly associated with subsequent death. This is not surprising when one considers that candidates for exercise testing do not have clinical evidence of significant left ventricular dysfunction; a much clearer relationship between ventricular arrhythmias and subsequent cardiac death has been established in patients with poor left ventricular function.[16]

In view of the uncertain predictive ability of exercise-related ventricular arrhythmias for subsequent cardiac events, the issue of whether or not to treat such patients with antiarrhythmic agents may be raised. Although common sense might dictate treatment, especially if the ectopy is accompanied by signs of myocardial ischemia, it should be recognized that the reproducibility of exercise-related ventricular arrhythmias is poor, and valid criteria by which to assess response to therapy are only just beginning to be defined. Moreover, the relationship between the presence and the type of ventricular arrhythmias and the threshold for sustained ventricular tachycardia or fibrillation must be appreciated because therapeutic serum levels of antiarrhythmic agents may raise the fibrillation threshold without appreciably influencing the presence of the ventricular arrhythmias and, conversely, ventricular arrhythmias may be suppressed without influencing the ventricular fibrillation threshold.

Blood Pressure Abnormalities

Effort-related hypotension—10 mm of mercury or greater fall in the systolic blood pressure or failure of the systolic blood pressure to increase by at least 10 mm of mercury—is an ominous finding that suggests the presence of underlying left main, severe left anterior descending, or triple-vessel coronary artery disease, with significant left ventricular dysfunction.[10] It often occurs in patients who have reduced effort tolerance and in whom anginal pain, dyspnea, or ST segment depression develops during exercise. Effort hypotension occurs in 10% to 25% of patients.[8,13,17] Its relative rarity may reflect the good functional class of patients undergoing postinfarction exercise testing, despite the presence of severe underlying multivessel coronary disease.

Starling and colleagues have addressed the prognostic value of an "inadequate" exercise blood pressure response,[8] defined as an increase of 10 mm of mercury or less or a decrease of 20 mm of mercury or more in systolic pressure or failure to achieve a peak systolic pressure exceeding 140 mm of mercury. Of 130 patients, 13% had an inadequate blood pressure response; in patients with subsequent cardiac death, recurrent MI, or the development of unstable angina, more than 60% had had an abnormal exercise blood pressure response. The prediction of cardiac death was enhanced by adding the abnormal blood pressure response to other manifestations of myocardial ischemia. Cardiac death occurred so infrequently, however, that the combination of variables failed to improve the predictive accuracy for death above 30%. Fioretti and co-workers found that failure to raise the systolic blood pressure at least 45 mm of mercury during exercise was the most sensitive predictor of mortality among all measured exercise test variables in 167 patients, occurring in all nonsurvivors of myocardial infarction observed for as long as 14 months.[12] Similarly, Krone and associates

described incidences of death or recurrent MI in 18% and 16%, respectively, of patients unable to reach an exercise systolic pressure of at least 110 mm of mercury, compared with 3% and 7% incidences, respectively, of these events in patients with higher achieved blood pressures.[14]

In evaluating the blood pressure response to exercise testing, the contributing role of nitrates, β- and calcium channel-blocking medication, and antihypertensive therapy must be taken into account. In patients receiving such therapy, valid prognostic statements cannot be made from the blood pressure response alone.

Whereas exercise hypotension has definite import for the postinfarction course and prognosis, effort hypertension does not appear to have a similar prognostic value. The finding of effort hypertension is of great clinical value, however, in that antihypertensive therapy may be begun in an effort to minimize myocardial oxygen demand in patients performing a given level of work after an MI.

Angiographic Correlations

Several laboratories have done coronary and left ventricular angiography around the time of hospital discharge and related the findings to exercise test responses.[18-20] In some series, a "normal" exercise test is associated with a high prevalence of disease confined to a single vessel, whereas in other series single-vessel disease was no more common than multivessel disease.[19,20] Patients who have symptoms or signs of myocardial ischemia, however, have usually been found to have severe multivessel coronary artery disease.[18,20] The ability to noninvasively detect patients who have a high probability of having severe coronary disease despite a functional class I or II level, and who might therefore be at risk for subsequent recurrent MI or cardiac death, validates the use of the predischarge exercise test as a prelude to further studies such as coronary angiography.

Applications of Nuclear Imaging Techniques

Adding nuclear imaging techniques to the predischarge exercise test enhances the sensitivity for the diagnosis of myocardial ischemia and can localize the ischemia to areas of myocardium subserved by specific coronary arteries. This information is not available from the exercise ECG (Figure 1). Imaging techniques can also help to detect patients who are at low risk for a cardiac event even if the exercise ECG is abnormal (Figure 2).[21] Thallium 201 can be easily used to show defects in isotope uptake resulting from inadequate myocardial perfusion in conjunction with test methods that involve dynamic exercise. Intravascular isotopes can be used easily in patients being tested by supine or upright bicycle ergometry to determine rest and exercise ejection fractions, ventricular end-diastolic and end-systolic volumes, and regional wall motion disorders.

The sensitivity of ^{201}Tl scintigraphy for detecting multivessel coronary disease varies with the severity of luminal obstruction,[19] being only about 20% for vessels having less than 70% obstruction, and 63% for vessels with more than 70% luminal narrowing. The ability, however, to detect the presence and location of ischemic myocardium is more important than establishing the presence of anatomic multivessel coronary disease because an anatomic pathologic process does not necessarily imply a functional pathologic process—that is, myocardial ischemia (Figure 2). The sensitivity of an "ischemic" ECG response to exercise or a reversible perfusion defect (or both) for detecting both multivessel coronary disease and "jeopardized" myocardium exceeds 80%[19]; the specificity of stress scintigraphy for detecting multivessel coronary disease also exceeds 80%. Stress scintigraphy might be especially useful in patients receiving digitalis preparations or β-blocking agents because valid ECG interpretation for myocardial ischemia is precluded in the former instance and the target heart rate, albeit submaximal, is often not achieved in the latter.

In addition to revealing fixed (infarction) and reversible (ischemia) perfusion defects, ^{201}Tl stress scintigraphy can also suggest the presence of unsuspected left ventricular dysfunction by demonstrating increased pulmonary uptake of the isotope.[22] Gibson and colleagues found that patients with lung uptake during postinfarction exercise testing had greater impairment of effort tolerance, higher incidences of dyspnea, angina, or ST segment depression, a greater number of perfusion defects, and lower resting ejection fractions than those without.[21]

The ability of stress scintigraphy to localize areas of jeopardized myocardium remote from the site of myocardial infarction has import for the meaning of the traditional ECG criteria for myocardial ischemia in such patients. The low predictive value of the electrocardiographic "ischemic response" for subsequent cardiac events based on exercise ST segment depression alone must result not only from the low prevalence of these events but also from the lack of specificity of this ECG abnormality for ongoing ischemia. ST segment depression in ECG leads remote from the acute MI may represent a reciprocal change rather than ischemia, thereby accounting for the benign course in many patients with this finding. Stress scintigraphy is a method by which the actual significance of exercise ST depression can be assessed: if reversible regional perfusion defects in areas remote from the MI are shown, ongoing ischemia is present; if reversible perfusion defects are not found, the ECG abnormalities are likely to represent reciprocal changes. Thus,

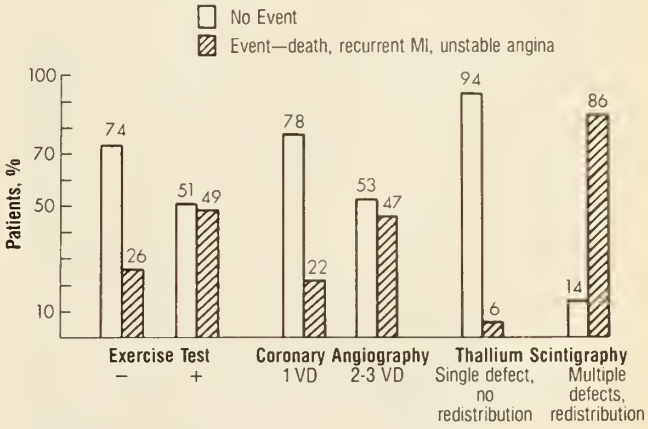

Figure 2.—The graphs show the comparative yields of the predischarge treadmill exercise test, coronary arteriography, and thallium 201 stress scintigraphy for predicting postinfarction cardiac events. In patients with a negative exercise test (−), single-vessel coronary artery disease (1 VD), or a single, fixed, perfusion defect without reperfusion to suggest ischemia, the one-year prognosis is good; note that the best separation of patients is accomplished using thallium scintigraphy. In contrast, in patients with a positive exercise test (+) or multivessel coronary artery disease (2-3 VD), the prediction of a cardiac event is relatively poor. Again, the best separation of patients according to their risk for events is accomplished by thallium scintigraphy (adapted from Gibson et al[21]). MI = myocardial infarction

stress scintigraphy not only enhances the ability to detect ongoing ischemia but also documents its absence, thereby identifying low-risk subgroups within the postinfarction population. In one important prospective study,[21] the results suggested that patients at especially low risk after an MI are those with a single regional perfusion defect, no redistribution of isotope over time, and the absence of lung uptake, whereas patients at high risk have multiple perfusion defects or pulmonary uptake of thallium or both. An important factor is that thallium scintigraphy discriminated low- and high-risk subgroups of patients better than did either exercise electrocardiography or coronary arteriography, due to the imperfect specificity of the former and the anatomic, rather than the functional, nature of the latter (Figure 2).

Thus, even though thallium stress scintigraphy is more costly than exercise electrocardiography alone, the potential benefits for optimal and cost-effective management following an MI probably justify the additional expense. The comparative yields of thallium scintigraphy carried out during low-level stress at discharge and during maximal exercise six to eight weeks later have not been explored in depth, nor has sufficient comparison been made of the relative predictive strengths of exercise variables between the two tests. Thus, if one wishes to do only a single exercise test, the optimum time to do so to accurately define prognosis remains uncertain.

In contrast to intracellular isotopes such as ^{201}Tl that show areas of diminished coronary blood flow, intravascular isotopes such as albumin labeled with technetium are used to assess intracardiac volumes and the ejection fraction. The findings of radionuclide ventriculography have been well correlated with those of contrast ventriculography done at cardiac catheterization. Exercise radionuclide ventriculography provides information regarding end-diastolic and end-systolic volumes and ejection fraction and may reveal reversible regional wall motion abnormalities reflecting areas of ischemic myocardium.[23,24] The ratio of arterial pressure to end-systolic volume, considered to represent an index of ventricular function independent of preload and afterload, which contribute to the calculated ejection fraction, can also be determined.

Corbett and colleagues assessed sensitivity, specificity, and the predictive value of predischarge exercise radionuclide ventriculography for the occurrence of death, recurrent MI, congestive heart failure, or postinfarction angina severe enough to require revascularization.[23] They found a substantially enhanced predictive value of this technique over the exercise ECG alone, especially for death and recurrent MI. Significant differences between patients sustaining a major cardiac event and those remaining event-free were a lower resting ejection fraction (44% versus 66%), a lower peak exercise ejection fraction (37% versus 76%), a greater number of regional wall motion abnormalities, higher resting end-diastolic and end-systolic volumes, a higher peak exercise end-systolic volume, and a subnormal increase in the pressure-volume index with exercise. The most severely depressed left ventricular function during exercise was generally found in patients with anterior transmural MI compared with inferior transmural MI or nontransmural MI of either anterior or inferior walls, although common exceptions indicated that ventricular performance is not entirely predictable from the location or extent of the myocardial infarction. Predischarge exercise left ventricular function was not predicted by clinical variables such as congestive heart failure or by exercise test variables suggesting myocardial ischemia. Similar overall results have been reported by others.[25]

Experience with exercise radionuclide ventriculography has been somewhat limited, due in part to logistic considerations. In addition, myocardial ischemia as the cause of abnormal exercise ventriculographic responses must be inferred rather than directly ascertained; cardiopulmonary stress must also be sufficient to provoke myocardial ischemia, a requirement that may not be met during bicycle exercise.

Patients who have had an MI who are not candidates for dynamic exercise testing because of musculoskeletal problems, pulmonary disease, or clinical congestive heart failure may be evaluated for myocardial ischemia by means of right atrial pacing or by dipyridamole-^{201}Tl scintigraphy. Both techniques have predictive capabilities similar to those of exercise testing.[26,27]

Resting Ejection Fraction

The prognosis after a myocardial infarction is directly related to the degree of left ventricular dysfunction—caused by the extent of MI as well as a previous MI. Clinical findings that suggest left ventricular dysfunction—congestive heart failure, an S_3 gallop—generally indicate a poor prognosis. The predictive power, however, of the absence of these findings for a benign course is far from perfect.

The resting left ventricular ejection fraction measured at the time of hospital discharge is considered by some investigators to be the variable most predictive of survival in patients with ischemic heart disease. Patients with an ejection fraction exceeding 40% have a low—2% to 5%—one-year mortality, those with an ejection fraction of 20% to 39% a 10% to 15% one-year mortality, and those with an ejection fraction of less than 20% a 45% to 50% one-year mortality. While the resting ejection fraction is reasonably well correlated with clinical and radiologic evidence of congestive heart failure, it is poorly correlated with a radiographic estimation of heart size: patients with no cardiomegaly on chest x-ray films may have an ejection fraction of well under 40%. Significant pulmonary congestion or pulmonary edema occurring during the acute—coronary care unit—phase of a myocardial infarction does not predict a depressed predischarge ejection fraction; as many as 30% of such patients may have a normal ejection fraction at the time of hospital discharge.[28] The relationship of the ejection fraction to ECG and enzymatic indices of infarct size varies and depends on whether there has been a previous infarction; whether the MI is right ventricular, contributing to an enzyme level rise but not necessarily to left ventricular dysfunction; whether the MI is transmural or nontransmural—which itself may be masked by a previous infarction—and whether there is continuing myocardial ischemia. Most infarctions associated with Q waves on the ECG produce segmental wall motion abnormalities. The extent and severity of the regional dyssynergy contribute directly to a global ejection fraction. Most major wall motion disorders—akinesis or dyskinesis—are associated with anterior wall infarctions, and the ejection fraction is not expected to change over time. A group of patients with MI has been identified[28,29] in whom pulmonary edema, reflecting acute severe left ventricular dysfunction, is present initially, but in whom the predischarge ejection fraction is normal; these patients may constitute as many as 30% of all patients presenting with pulmonary edema and

acute MI.[28] The first-year mortality in this patient group is about 20%, lower than the 25% to 45% first-year mortality in patients with both pulmonary edema and a depressed ejection fraction, but considerably higher than the 5% mortality in patients with no pulmonary edema and a normal predischarge ejection fraction. These observations may be explained by postulating transient ischemic dysfunction occurring at the time of infarction, with subsequent recovery sufficient to result in a normal ejection fraction some time later. The cause of the poor prognosis is recurrent ischemia, usually due to extensive multivessel coronary artery disease.

Recent data suggest that the end-systolic volume (ESV) may be superior to the ejection fraction as a high-risk indicator, especially if the ejection fraction is less than 50%.[30] In one series of 120 patients with ejection fractions of 40% to 49%, 30% of patients with an ESV exceeding 95 ml died compared with 10% of patients with an ESV of less than 95 ml.[30] Similarly, in 106 patients with ejection fractions of less than 40%, 40% of patients with an ESV exceeding 130 ml died within three years compared with 20% of those with an ESV of less than 130 ml.

Ascertaining those patients at high risk from severe ventricular functional impairment warrants aggressive medical management of associated problems such as ventricular arrhythmias and recurrent congestive heart failure and consideration for revascularization if the ventricular dysfunction is found to be caused or contributed to by ischemia.

Ventricular Arrhythmias

Observations made early in the 1970s suggested that ventricular extrasystolic activity in survivors of myocardial infarction was associated with a greater risk of subsequent cardiac mortality, including sudden cardiac death. Ambulatory electrocardiographic monitoring at the time of hospital discharge is currently used to detect significant ventricular arrhythmias. Criteria for "simple"—or "benign"—and "complex" ventricular arrhythmias have been derived to more clearly delineate those patients at highest risk.[31,32] "Simple" ectopy refers to unimorphic ventricular depolarizations occurring relatively infrequently—less than ten an hour, although criteria vary substantially. "Complex" ectopy refers to multimorphic ventricular depolarizations, triplets, salvoes, and sustained—more than 30 consecutive complexes—ventricular tachycardia.

Several studies show a relationship of complex ventricular arrhythmias to subsequent cardiac mortality, especially in the first year after an MI,[32-34] but the strength of the association varies. This can be explained in part by variations in study designs that include differences in the total number of patients studied, in the proportions of men and women making up the study group, and in the number of hours of ambulatory ECG monitoring. Other differences in these studies were in the exclusion of patients older than a certain age (so as to ensure a complete follow-up), in the definition of sudden death, and in the role of the use of antiarrhythmic, β-blocking, and digitalis therapy.

Ventricular Tachycardia

Most investigators define ventricular tachycardia as three or more consecutive ventricular extrasystoles occurring at a rate exceeding 100 or 120 beats per minute.[35,36] Defined as such, several observations have been made about its occurrence on predischarge ambulatory ECG monitoring.

- Episodes of ventricular tachycardia tend to occur in patients who also have frequent and complex ventricular ectopy,[36,37] but in many patients they occur only once in a 24-hour period.
- The incidence varies with the number of hours of recording.
- The number of ventricular complexes in each episode of tachycardia varies considerably but rarely exceeds 20 consecutive complexes.
- Most episodes are unaccompanied by symptoms, probably because of their brevity.[36]
- R-on-T premature ventricular extrasystoles do not lead to ventricular tachycardia.
- The tachycardia does not degenerate into ventricular fibrillation.
- Neither the occurrence nor the rate of the ventricular tachycardia is closely related to the underlying or immediately preceding sinus rate.
- Its occurrence may not per se predict either sudden cardiac death or recurrent MI; the increase in cardiac mortality in patients with ventricular tachycardia may reflect its frequent association with a higher functional classification, previous infarctions, and a history of congestive heart failure.

The issue of whether ventricular tachycardia per se predicts subsequent death remains controversial. Two-year mortality in patients with ventricular ectopy at the time of hospital discharge has been reported as 8%, 16%, and 37%, respectively, in patients with less than three ventricular extrasystoles per hour, those with more than three extrasystoles per hour or at least three consecutive extrasystoles, and those with more than three extrasystoles per hour and at least three consecutive extrasystoles,[3] further emphasizing the complexity of the issue. The number of patients with ventricular tachycardia and the number of deaths in a given follow-up period are relatively small, making interpretation of the significance of the association uncertain. Moreover, the role of antiarrhythmic therapy, digitalis, and β-blockade therapy as treatment for postinfarction angina or prophylaxis against recurrent MI—rather than as antiarrhythmic therapy—is difficult to delineate. Thus, antiarrhythmic therapy to suppress ventricular tachycardia may not be warranted; on the other hand, treatment of complex ventricular arrhythmias—which include tachycardia—may have a rational basis. Firm recommendations cannot be offered at the present time, although studies in progress should provide guidelines when completed.

An interesting study published recently suggested that the import of ventricular arrhythmias is different in patients with "non-Q wave" MI compared with those with "Q wave" MI.[38] Because in earlier studies patient populations were not divided according to these ECG criteria, these observations are unique. In those with non-Q wave MI, complex ventricular arrhythmias were present in 69% of nonsurvivors but in only 39% of survivors at one year. These differences were not present in patients with Q wave MI, regardless of the site of infarction. Survival data showed that patients without complex ventricular arrhythmias had a greater than 90% one-year survival regardless of whether Q wave or non-Q wave MI had occurred; in sharp contrast, however, patients with complex ventricular arrhythmias and non-Q wave MI had a 73% one-year survival compared with a 90% survival in patients with complex arrhythmias and Q wave MI. Thus,

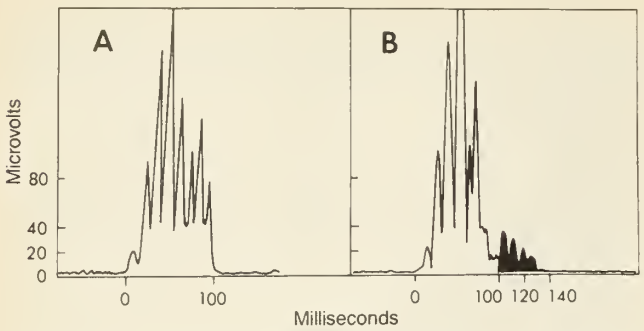

Figure 3.—The schematic drawing shows a normal signal-averaged QRS complex **(A)** and an abnormal one **(B)**. The abnormal complex is prolonged and displays low-amplitude signals, below 40 μV (shaded area). This pattern might indicate underlying inhomogeneity of ventricular depolarization and repolarization, the electrophysiologic substrate for ventricular arrhythmias. The pattern might therefore serve as a marker for patients with inducible ventricular tachycardia.

electrical instability might have greater prognostic significance in patients with non-Q wave MI and might lead to a stronger consideration for antiarrhythmic treatment.

Several issues regarding the information obtained from predischarge ambulatory ECG monitoring remained unresolved. Should patients with *any* frequency of ventricular arrhythmias receive antiarrhythmic medication, or only those with a certain frequency? Should treatment be reserved for patients with complex ventricular arrhythmias and depressed ejection fractions, considered to be at highest risk? In this regard, the ejection fraction may be of less predictive strength in patients with non-Q wave MI,[38] with arrhythmias conferring risk even if the ejection fraction is normal. What are the criteria for the adequacy of therapy?—plasma drug concentration or the suppression of ventricular arrhythmias? Is suppression of all ventricular arrhythmias a rational goal, or should it be suppression of only complex forms? How long should antiarrhythmic therapy be continued? What criteria should be applied for terminating antiarrhythmic therapy? How often should ambulatory ECG monitoring be done? Finally, what is the relationship between complex ventricular arrhythmias and ventricular fibrillation? Does antiarrhythmic therapy that suppresses the one protect against the other? Does the presence of one even predict the other? And, finally, is a "therapeutic" serum concentration of an antiarrhythmic agent sufficient to protect against ventricular fibrillation while having minimal overall effect on ventricular arrhythmias?[39] Few studies provide data allowing rational decision making on these issues. Answers to these questions may become apparent from future controlled investigations in large numbers of patients.

The role of electrophysiologic testing before hospital discharge has also been evaluated as a tool for predicting the risk of subsequent cardiac death.[40-43] The data from several available studies indicate that ventricular tachycardia can be induced in about 25% of patients who have had an MI, many of whom do not have significant ventricular ectopy on ambulatory ECG monitoring. Although these studies report that from 20% to 79% of these patients do not survive the first year after an MI, the consensus is that electrophysiologic testing cannot accurately predict death. The many discrepancies among the reported studies no doubt relate to the use of different stimulation protocols; nonuniform definitions of sustained and nonsustained ventricular tachycardia; different patient populations; concomitant antiarrhythmic drug therapy or drug therapy initiated during the follow-up period; the use of β-blocking drugs for hypertension, angina, or as prophylaxis against recurrent MI; intercurrent cardiac events; and myocardial revascularization procedures. Moreover, patients with ongoing ischemia or severe left ventricular dysfunction (or both), who are precisely the ones at highest risk for an arrhythmic event, are almost always excluded from electrophysiologic study.

The most recent advance in this area is the development of the signal-averaged ECG. By filtering the QRS complex recorded from the body surface, the presence and absence of "late potentials" can be discerned (Figure 3). These late potentials occur 100 to 120 ms after the QRS onset and are of low amplitude (less than 40 μV). Their presence and specific characteristics correlate with ventricular tachycardia induced in an electrophysiologic laboratory and thus perhaps also with sudden death. Although in its infancy, this technique may come to serve as a screening test after an MI for patients who might benefit from electrophysiologic investigation.

Summary

The ability to assess the risk of postinfarction patients for the development of subsequent reinfarction, unstable angina requiring myocardial revascularization, and cardiac death allows appropriate management strategies to be developed at the time of hospital discharge. At San Francisco General Hospital, all patients recovering from myocardial infarction undergo 24-hour ambulatory ECG monitoring before hospital discharge. Antiarrhythmic agents are generally used in patients with complex ventricular ectopy who have the additional risks of a depressed resting ejection fraction or overt congestive heart failure and, in some cases, ongoing ischemia. Electrophysiologic studies are not undertaken in these patients. Exercise tests are done in appropriate patients to document the presence of myocardial ischemia, with particular emphasis on areas remote from the infarction, a situation best assessed at the present time by using ^{201}Tl scintigraphy. Remote ischemia indicates the presence of significant multivessel coronary disease, and its finding warrants coronary arteriography to assess candidacy for myocardial revascularization or, in patients in whom this is unwanted or undesirable, for aggressive anti-ischemic therapy. In patients with no evidence of ischemia at the time of hospital discharge, a maximal exercise test is done six to eight weeks later to evaluate effort tolerance as well as the interim development of ischemia.

Finally, in patients who do not have overt congestive heart failure, a resting left ventricular ejection fraction is measured to evaluate overall ventricular function; this is particularly important in patients in functional classes I and II because left ventricular dysfunction may not be clinically apparent. A finding of left ventricular dysfunction unrelated to ischemia warrants medical management, whereas that contributed to by ongoing ischemia warrants consideration for coronary arteriography and myocardial revascularization.

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Epitomes
Important Advances in Clinical Medicine

Anesthesiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in anesthesiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Regional Anesthesia in Children

REGIONAL ANESTHESIA has been used in children since the early 20th century but with little application by most anesthesiologists. In the past five years interest in the pediatric use of regional anesthesia has increased, paralleling the trend toward that of local and regional anesthesia in adults, the heightened awareness of the need to provide more reliable and effective postoperative analgesia, the availability of long-acting drugs for local anesthesia, and of the spinal administration of narcotics.

Relieving postoperative pain is the most common indication for using regional anesthesia in children. Effective pain relief by regional blockade reduces the risk of wound bleeding or dislodgment of dressings or drains postoperatively, and allows a body part to be immobilized after delicate reconstructive operations. Postoperative narcotic requirements are reduced or eliminated, with an attendant reduction of risk, side effects, and demands on nursing time. Patient and parent satisfaction is high, and psychologic trauma is reduced.

Regional anesthesia is frequently used in combination with light levels of general anesthesia. This combination results in excellent operating conditions without the use of neuromuscular relaxants and reduces the requirement for the general anesthetic agent. This technique is particularly suited to patients with altered pharmacokinetics due to hepatic dysfunction or renal failure. A rapid return of consciousness and recovery of airway reflexes are assured.

Using regional anesthesia may eliminate the need for general anesthesia, particularly for peripheral procedures. For example, a child with a myopathy or malignant hyperthermia is an ideal candidate for regional anesthesia combined with light, intravenously administered sedation for procedures such as muscle biopsy.

Regional blocks may be divided into two broad groups—central and peripheral. Central blocks include caudal, lumbar or thoracic epidural, and subarachnoid blocks (spinal anesthesia). Peripheral blocks include brachial plexus, ilioinguinal or iliohypogastric nerve, femoral nerve, and sciatic nerve blocks. Any of these may be done in children.

The most common regional technique used in pediatric anesthesia is the sacral epidural or caudal block. Experience has shown it to be an easy and reliable method with proven efficacy and safety. Lumbar epidural anesthesia is used routinely in many European and Australian centers, but more widespread acceptance in this country awaits the availability of pediatric-sized epidural needles, which are commercially available abroad. Bupivacaine hydrochloride is usually chosen for caudal or lumbar epidural anesthesia. A total dose of 2 to 3 mg per kg of body weight (1 ml per kg of a 0.25% solution) reliably provides analgesia to midthoracic dermatomes and motor blockade of varying intensity, with a duration of four to eight hours. While this is a rather large dose compared with what would be administered to an adult, peak bupivacaine plasma levels remain well below the toxic threshold when the total dose is 3 mg per kg.

The epidural use of morphine has been evaluated in children and has been shown to effectively provide prolonged analgesia. The risk of delayed respiratory depression exists in children as in adults and mandates a careful monitoring of children following epidural narcotic administration. We recommend a 24-hour period of observation and monitoring following each dose. The effective dose of epidural morphine is 0.033 to 0.1 mg per kg.

A subarachnoid block with tetracaine may be used for inguinal herniorrhaphy or a similar procedure in newborn infants. A subarachnoid block may be established in an awake infant using only local anesthesia, and often there is no additional need for drugs that depress the central nervous system. Spinal anesthesia using tetracaine and epinephrine has a shorter duration—100 minutes— in newborns compared with adults. Hypotension rarely occurs in children after establishing a central regional block, even without prior volume loading with intravenous fluids.

Peripheral nerve blocks are best done during deep sedation or general anesthesia in children. They have the advantage of providing a more localized area of anesthesia with smaller doses of drugs, but they have a higher failure rate and carry a small risk of needle trauma to neurovascular structures. These disadvantages may be minimized during brachial plexus or sciatic nerve blocks with the use of an electrical nerve stimulator to aid in localizing the target nerve bundle. As is the case for epidural blocks, therapeutic doses of bupivacaine—2 to 3 mg per kg—result in safe plasma drug concentrations following either femoral nerve or brachial

plexus block in children; the plasma concentrations are less than would be expected were the same dose given to an adult.

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Continuous Noninvasive Arterial Monitoring

NONINVASIVE, real-time, beat-to-beat arterial blood pressure measurement has recently become available through new monitoring technology. It is now possible to measure the finger arterial blood pressure continuously with a finger cuff without using any type of cannula or invasive device. This technique uses photoplethysmography and was first described in 1973 by Penaz. Currently, the only commercially available unit for noninvasively monitoring finger arterial blood pressure is the Finapres (*fin*ger-*a*rterial-*pres*sure) by Ohmeda. This monitor has been extensively tested for accuracy and reliability in a variety of clinical situations. The Finapres monitor provides a waveform resembling the pressure waveform achieved through radial artery cannulation. This device also provides digital readouts on systolic, mean, and diastolic blood pressures and the pulse rate. Although the Penaz method does not replace an arterial line in all situations, it does not carry the documented risks of arterial cannulation such as thrombosis, embolization, infection, or nerve injury. Neuropraxia has also been theorized as a potential complication of this monitor because it uses a finger cuff that impedes venous return; no complications have been seen in clinical experience with more than 1,000 patients, however. This type of monitoring may be useful in the surgery suite during anesthesia and in critical care areas, especially when few or no arterial blood specimens need to be drawn.

The Penaz method uses a small, specially designed finger cuff containing an infrared light source and photocell detector to determine the blood volume of the finger by detecting absorbency at a wavelength specific for hemoglobin. Changes in hemoglobin saturation do not affect blood pressure readings. This photoplethysmographic unit is linked to an electropneumatic transducer and a fast-reacting servosystem that includes a computer microprocessor to analyze arterial waveforms. An elegant feedback loop connects the components. Adjustments are made almost instantaneously with changes in blood pressure—and thus finger blood volume—and are relayed to the monitor and displayed as the arterial pressure waveform. Recalibration occurs once a minute to identify and correct for alterations in vascular smooth muscle tone.

In a clinical trial comparing two Ohmeda prototypes with intraarterial monitoring, pressure changes were accurately and linearly reproduced over a wide range of mean arterial pressures from 2 to 164 mm of mercury (0.27 to 21.81 kilopascals). These prototypes functioned well most of the time, and accuracy was good. When the monitors did not function, the machines showed an error message. There were no falsely normal or high readings when blood pressures were low. High and low blood pressures were measured with equal accuracy. It has also been reported that noninvasive arterial measurements are typically lower than those seen with a radial artery catheter. The person's hand should be at heart level for greatest accuracy, as with arterial pressure transducers. Readings from the thumb using a special blood pressure cuff may be more reliable because the thumb is closer to the radial artery.

Blood pressure measurements by the Penaz method may be inaccurate due to technical problems or physiologic abnormalities produced by drugs, neurohumoral factors, temperature, and local factors such as vascular disease and anatomic abnormalities. This device, however, has been found to work well in most patients with peripheral vascular disease, during peripheral vasoconstriction, and during open-heart procedures under hypothermic conditions on cardiopulmonary bypass. The device alerts practitioners to incorrect readings by emitting an error signal in most cases.

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Anesthesia for Preterm Neonates

IN A LETTER to the magazine *Birth* (June 1986), a mother complained that her preterm child had been subjected to a surgical procedure without anesthesia. As a result, a storm of protests occurred in the lay and medical media. This review presents the current status of anesthesia for preterm neonates.

In the past decade, the survival of premature infants has increased tremendously, especially of those weighing less than 1,000 grams. A large number of these surviving babies have undergone operations under paralysis with either inadequate or no anesthesia.

These babies are usually ill, severely fluid restricted, and possibly receiving potent diuretics. In the early 1970s, as these babies were being saved, monitoring techniques were rudimentary. Halothane was the principal agent, and bradycardia, hypotension, and intraoperative deaths were common. The rationale for "relaxant anesthesia" was that due to immaturity of the nervous system, these infants neither feel nor remember pain. It was widely believed that these babies do not need anesthesia and, in fact, they may not tolerate general anesthesia.

Recent work has shown that as early as the 13th to 20th weeks, there is evidence of the anatomic requirements for pain perception. Evoked potentials and cerebral glucose metabolism offer evidence of functional maturity. Responses such as changes in pulse and blood pressure, crying, and

grimacing have been quantified for circumcisions done without anesthesia. Spectrographic properties of crying associated with pain have been identified. Preterm babies anesthetized with the use of nitrous oxide and curare had a greater stress response to a surgical procedure than babies receiving nitrous oxide, curare, and fentanyl. Finally, evidence has been presented of possible short- and long-term memories of pain.

With new monitoring and anesthetic techniques, most preterm neonates can be safely anesthetized. Techniques reported include the use of medium to high doses of the narcotic fentanyl, the inhalational agent isoflurane, or regional anesthesia.

Anesthesiologists today agree that general or regional anesthesia should be considered for all neonates undergoing an operation. On occasion, physiologic instability may demand that the doses of anesthetic agents be reduced or their use discontinued. This decision should not be based solely on an infant's age or perceived degree of maturity.

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Malignant Hyperthermia—Update

MALIGNANT HYPERTHERMIA is an acute hypermetabolic syndrome that can progress within 30 minutes to a premorbid state in which the arterial pH is as low as 6.6 units and the temperature is above 42°C (108°F). Until recently, malignant hyperthermia was among the leading causes of anesthetic death, with mortality above 65%.

The incidence of malignant hyperthermic crises is about 1 per 14,000 anesthetics, but the population at risk may be as high as 1 per 200. The syndrome is multigenetic, with variable expressivity and incomplete penetrance. The only well-documented triggering agents in humans are succinylcholine chloride and the potent inhalation anesthetics.

About 1% of children induced with halothane and succinylcholine will display masseter spasm, and half of those children are susceptible to malignant hyperthermia. The first symptoms of a crisis presenting during anesthesia are hypercarbia, sinus tachycardia, and tachypnea. Next, skin becomes mottled with cyanotic areas and patches of bright red flushing, after which generalized, rigor mortis-like skeletal muscle rigidity may occur. Fever is a late sign.

Triggering of susceptible muscle takes place during excitation-contraction coupling. Once susceptible muscle has been triggered, a contraction is maintained by an abnormally increased phospholipase A_2 activity, which causes an increase in mitochondrial free fatty acid content and stimulates calcium release. In the presence of free fatty acid, sarcoplasmic reticulum calcium release is increased and reuptake is inhibited. The resulting high sarcoplasmic calcium concentration allows actin and myosin fibers to interact. In late stages, when the muscle temperature rises above 43.5°C (110°F), actin-myosin binding is no longer calcium-dependent and the muscle contraction becomes an irreversible contracture.

Treatment should include discontinuing the use of the triggering drugs, hyperventilating the patient with 100% oxygen, and administering 2.5 mg per kg of body weight of dantrolene sodium intravenously as quickly as possible. Additional doses of 2.5 mg per kg should be administered intravenously, to a maximum of 10 mg per kg until symptoms resolve.

Dantrolene inhibits excitation-contraction coupling, but its major action appears to be on the sarcoplasmic reticulum. It increases the contraction activation threshold voltage in susceptible and normal muscle and prevents the depolarization of susceptible muscle by halothane.

The in vitro caffeine-halothane contraction test is the only widely accepted test for malignant hyperthermia. The diagnosis is established by evaluating a fresh, intact muscle segment for contraction in response to halothane and caffeine, which have little effect on normal muscle.

Elective surgical procedures are not contraindicated in patients known to be susceptible. Any type of conduction anesthesia, using any type of anesthetic for local effects (including amides) is acceptable. General anesthesia can be safely administered using a balanced technique combining nitrous oxide and narcotics augmented by nondepolarizing muscle relaxants. Other safe drugs include barbiturates, benzodiazepines, and ketamine hydrochloride. Some physicians preoperatively administer intravenous dantrolene as a prophylactic measure, while others believe it unnecessary. The Malignant Hyperthermia Association of the United States (PO Box 3231, Darien, CT 06820, [203] 655-3007) maintains a 24-hour physician referral service.

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Perioperative Myocardial Infarction

OF THE 20 MILLION PATIENTS presenting each year for anesthesia and surgical treatment in the United States, about 1 million have documented coronary artery disease, 2 million have two or more major risk factors for coronary artery disease, and 6 million are older than 65 years. Despite numerous advances in monitoring and therapeutic techniques, the incidence of perioperative myocardial infarction in patients undergoing noncardiac operations remains high: 6% in patients with a previous infarction, 10% in patients undergoing major vascular surgical intervention, and 37% in patients with a recent infarction. In 1983 it was suggested that the reinfarction rate was lower using invasive intraoperative monitoring (2% versus 6%) and prolonged intensive care unit stay (6% versus 37%). These results, however, have not been independently confirmed over the past five years.

Over the next decade, the challenge will be to lower perioperative cardiac morbidity. The solution is to rigorously identify the predictors of morbidity and, once identified, attempt to therapeutically alter them. Unfortunately, there are only a few thorough outcome studies of perioperative

cardiac morbidity, and only a limited number of predictors are known. The established preoperative predictors are a recent—less than six months—myocardial infarction, current congestive heart failure, and, perhaps, instability of the anginal pattern. Such predictors as age, hypertension, diabetes mellitus, and stable angina remain controversial. The use of specialized preoperative testing remains controversial as well, although dipyridamole-thallium imaging has shown recent promise. Intraoperative tachycardia and hypotension are important predictors of outcome. In addition, it has been recently suggested that intraoperative myocardial ischemia may be an important predictor, but these studies were done in patients undergoing a coronary bypass operation, making interpretation difficult. Major body cavity operations and emergency surgical interventions also appear to place patients at higher risk, but neither the type nor the duration of anesthesia appears to play a significant role. Other advances include the finding that electrocardiographic ST abnormalities are best detected in leads V_5 (75%), V_4 (additional 15%), and II (additional 6%). Until this year, little was known of the postoperative risk factors. Recently a significant incidence of postoperative myocardial ischemia was shown compared with either intraoperative or preoperative ischemia. In addition, high heart rates were found during this particular period, which might play a causal role with respect to the ischemic pattern. Thus, the detection and aggressive treatment of both tachycardia and ischemia occurring in the postoperative period may play an important role in reducing the incidence of perioperative myocardial infarction.

In conclusion, this disorder remains a significant problem in the United States; only a few predictors from the preoperative, intraoperative, and postoperative periods have been identified, however. The challenge we face in the 1980s and 1990s is similar to that faced by coronary artery disease investigators in the 1950s. Only when predictors of coronary artery disease were identified (by studies like that in Framingham, Massachusetts) could rational approaches to prevention and treatment be devised and morbidity therefore reduced. This approach must be applied to the study of perioperative cardiac morbidity if significant advances in clinical care are to be made.

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Perianesthetic Temperature Regulation and Postoperative Tremor

ANESTHETIZED PATIENTS are generally thought to be poikilothermic, which results in hypothermia during exposure to cold operating rooms. Following a surgical procedure, anesthetic concentrations in the brain decrease rapidly and normal thermoregulatory responses to cold are expected. Thus, conventional theories of thermoregulation predict that after an operation, a patient with hypothermia will feel cold and compensate with peripheral vasoconstriction and shivering. Recent evidence suggests that thermoregulatory responses to cold do occur during anesthesia and that postoperative "shivering" is not generally thermoregulatory.

Intraoperative temperatures usually decrease for one to three hours and then change little for the duration of an operation. Thermal steady state occurs when metabolic heat production equals environmental heat loss; this can occur passively (no specific regulation) or from active thermoregulation (vasoconstriction and nonshivering thermogenesis). Patients undergoing short operations who remain relatively warm—35°C (95°F) or higher—achieve thermal steady state from a passive interaction with the environment. Patients undergoing lengthy operations who become hypothermic—about 34.5°C (94°F)—display profound peripheral vasoconstriction; those who are kept normothermic do not. Thus, vasoconstriction in such hypothermic patients is a direct response to intraoperative hypothermia. Once vasoconstriction occurs, core temperatures do not usually decrease further because vasoconstriction limits heat loss to the environment.

Body temperature is normally controlled by the hypothalamus, which responds to thermal input from every part of the body. This regulatory system is frequently modeled as a "setpoint" because the threshold temperatures that activate responses to hypothermia and to hyperthermia differ by only about 0.1°C. Thermoregulatory vasoconstriction, however, does not occur intraoperatively until core temperatures are about 2.5°C (5°F) below normal, indicating that the threshold temperature causing activation of regulatory responses to hypothermia is substantially decreased. It is unlikely that the hyperthermic threshold temperature decreases similarly because normothermic patients do not sweat, as would be expected were their core temperatures 2.5°C above the hyperthermic response threshold. It is also unlikely that the hyperthermic threshold remains unchanged, as anesthetized animals and humans become hyperthermic in warm environments. Most probably, anesthetics increase the hyperthermic threshold, resulting in a wide temperature range over which thermoregulatory responses are absent.

Postoperative tremor is commonly attributed to normal thermoregulatory shivering in response to intraoperative hypothermia. Postoperative "shivering," however, frequently does not occur in hypothermic patients, and, when it does, it is rarely associated with vasoconstriction, although vasoconstriction is a universal feature of thermoregulatory shivering. Moreover, shivering frequently occurs in normothermic patients after an operation, a finding difficult to reconcile with conventional theories of thermoregulation.

The electromyographic patterns of postoperative tremor do not resemble normal thermoregulatory shivering. One pattern is a regular, bursting, 5- to 7-Hz activity that is identical to both pathologic clonus and clonus produced by plantar flexion during recovery. The second pattern is tonic, but differs from shivering because it does not occur in all muscles simultaneously; does not show the typical, slow four-to-six-cycles-per-minute waxing and waning pattern; and has a strong 5- to 7-Hz underlying driving activity.

Postoperative tremor also does not correlate with core temperature, as would be expected if the tremor were thermoregulatory. Instead, its clonic pattern is highly correlated with end-tidal isoflurane concentration. Clonus generally occurs when descending cortical control does not inhibit spinal cord reflexes. During anesthesia, it is probable that spinal cord function returns before effective descending cortical control is reestablished. (The brain is "asleep" and the

spinal cord is "awake," producing a functional spinal cord transection.) These results suggest that inadequate descending control of spinal reflexes, not thermoregulatory shivering, is the cause of postoperative tremor.

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Postretrobulbar Apnea Syndrome

THE RETROBULBAR ADMINISTRATION of anesthetics is an effective method of achieving regional anesthesia and akinesia for many types of eye operations. Ocular complications are unusual but include retrobulbar hemorrhage, central retinal artery occlusion, and perforation of the globe or optic nerve. The retrobulbar administration of local anesthesia has also been associated with episodes of apnea, on occasion progressing to cardiopulmonary arrest.

Possible explanations of respiratory arrest following retrobulbar block include oversedation, intravascular injection (intravenous or retrograde arterial), subdural injection, or an idiosyncratic drug reaction. Opinion is varied as to which mechanism is responsible. One of the first cases reported was of a patient who suffered an immediate cardiopulmonary arrest after the retrobulbar administration of 2 ml of a 1:1 mixture of 0.5% bupivacaine hydrochloride and 2% mepivacaine hydrochloride. The reaction was explained as an intravascular injection into the ophthalmic artery that traveled in a retrograde fashion to the internal carotid artery and then progressed antegrade to the midbrain structures, resulting in respiratory arrest.

Another four cases of apnea following retrobulbar block have been reported and the possibility suggested that an injection into the optic nerve allowed direct access to midbrain structures. It has been shown radiographically that a retrobulbar injection into the dural sheath of the optic nerve results in diffusion of contrast material into the subarachnoid space surrounding the pons and midbrain. If anesthetics were similarly injected, they could bathe the respiratory centers, resulting in brain-stem anesthesia and subsequent apnea.

Respiratory arrest following retrobulbar placement of an anesthetic is a potentially life-threatening problem. Experimental evidence exists supporting two independent mechanisms: intravascular injection or injection into the optic nerve sheath. Regardless of the pathway, cardiac and neurologic sequelae can be avoided if appropriate management of the airway is initiated and proper ventilatory support is maintained. Patients having eye operations under regional anesthesia must be adequately monitored after a retrobulbar injection. Emergency equipment and personnel trained in cardiopulmonary resuscitation should be readily available.

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Chin GN, Almquist HT: Bupivacaine and lidocaine retrobulbar anesthesia: A double-blind clinical study. Ophthalmology 1983; 90:369-372

New Methods of Measuring Respiratory and Anesthetic Gases

RECENT DEVELOPMENTS in measuring respiratory and anesthetic gases promise to improve the safety and efficacy in monitoring patients undergoing anesthesia. These developments constitute both improvements in current equipment and the availability of new ways of measurement.

Why is measuring respiratory and anesthetic gases important to anesthesiologists? A large portion of anesthetic accidents are from anesthetic overdose or the failure to oxygenate or ventilate an anesthetized patient. The most important step in preventing anesthetic accidents is the rapid recognition of these critical events. Such problems may often be detected before injury of the patient by continuous monitoring of the gases in the breathing circuit. The measurement of gases in the operating room, however, has suffered from a lack of affordable, dependable technology capable of measuring all gases of interest in a continuous fashion.

Oxygen, the most commonly measured gas, has been monitored with polarographic devices that have a slow response time and a three- to six-month usable life. These sensors suffer frequently from calibration errors. Paramagnetic oxygen sensors are now available that have a response time fast enough to delineate inspired and expired oxygen concentrations. They have no consumable parts, are self-calibrating, and do not have cross sensitivity to the anesthetic agents. The initial cost is much more than that for currently used devices, but this may be compensated over time by replacement costs and reliability.

Expired carbon dioxide is measured most commonly by infrared spectroscopy. Volatile anesthetic agents have also been measured using infrared devices. This technology has suffered from calibration errors related to nitrous oxide concentration and humidity and a relatively slow response time for measuring the anesthetic agents. New digital processing methods have solved many of the calibration and cross-sensitivity problems inherent in these devices, making them more reliable and cost competitive.

The mass spectrometer has the ability to measure all of the gases of interest but has been so expensive that multiplexed systems were required in order to be affordable. Present problems with shared systems include limited sampling time and sample delays, poor reproduction of waveforms due to long sampling lines, and blockage of sampling lines. The mass spectrometer may also be disrupted for long periods of time by helium used in some laser procedures and propellants in inhalants used for treating asthma. New mass spectrometers are now available for single-patient use. They should solve many of the problems inherent in shared systems.

Raman spectroscopy represents the most significant new development in continuous gas monitoring. It measures gas concentrations by exciting the gas molecule with a laser and measuring the intensity of the scattered light emitted when the molecule returns to the unexcited state. The frequencies emitted by the molecule give a specific chemical identification of the gas. This instrument has been tested against a dedicated mass spectrometer and was shown to be equally accurate in both bench testing and clinical use. It is self-calibrating and has a rapid response time. The device is theoretically more durable than the mass spectrometer and is not disrupted by helium. The instrument offers a dedicated, du-

rable, self-calibrating analyzer, which measures all of the gases of interest.

This newly available range of gas monitoring instrumentation is reliable, relatively cost-effective, and provides anesthesiologists with continuous on-line data. By alerting anesthesiologists to potentially adverse events during an operation at an early stage, these new technologies offer the hope of improved care and decreased morbidity and mortality.

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Chemical Basis for the TURP Syndrome

An array of hemodynamic and central nervous system (CNS) abnormalities has been described in some patients following transurethral resection of the prostate (TURP). The hemodynamic abnormalities include cardiac arrhythmias, hypotension, and even cardiovascular collapse, while the CNS abnormalities include confusion, transient blindness, seizures, and even coma. In the past these manifestations have been collectively called the "TURP syndrome" and have been generally attributed to dilutional hyponatremia and water intoxication from absorbing an excessive amount of irrigating solution during the surgical resection of the prostate gland. Absorption of 4 to 8 liters of sodium-free irrigating solution has been documented with dilution of the plasma sodium level down to nearly 100 mEq per liter. Because the sodium ion is necessary for depolarizing cells and for maintaining extracellular osmolality, hyponatremia is obviously presumed to be the cause of abnormal electrophysiologic responses of the CNS and the heart. Recent data suggest, however, that the absorption of glycine, the osmolar substance in the irrigating solution commonly used during TURP, may contribute to the TURP syndrome.

Glycine 1.5% is the most widely used irrigant because it is thought to be an effective osmotic replacement for sodium ions and to be nontoxic to the body. Glycine 1.5%, however, is slightly hypo-osmolar, being about 200 mosm per liter. Glycine is a nonessential amino acid with a normal plasma level of 13 to 17 mg per liter. It readily crosses the blood-brain barrier and is an inhibitory transmitter in the spinal cord and in the synapses of the medulla, pons, tectum, and retina. Glycine has been shown to suppress the waveforms of both the electroretinogram and visual evoked potentials in rabbits.

More recently we have found that glycine, in quantities capable of being absorbed clinically—about 9,000 μmol per liter—can alter both the amplitude and the latency of visual evoked potential waves in anesthetized dogs. Cardiac output and mean arterial blood pressure were also depressed by glycine in this laboratory model. Ammonia, a biotransformed metabolite of glycine, has been suggested as another potential neural toxic agent. Although the vast majority of patients subjected to a transurethral resection of the prostate do not manifest significant CNS abnormalities, we have shown in patients who complained of visual and other CNS disturbances the presence of hyponatremia, hyperglycinemia, and hyperammonemia. The administration of hypertonic saline in patients with adequate renal function remains the treatment of choice for patients exhibiting the TURP syndrome. As yet, there has been no report of permanent visual disturbance, but clinicians should be aware of a chemical basis for the TURP syndrome in addition to hyponatremia and water intoxication.

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Editorials

On Specialized Centers for Patient Care

ELSEWHERE IN THIS ISSUE Rosenblatt and co-workers report on the apparent success of regionalization of perinatal care in the state of Washington, with the care of underweight and presumably higher risk babies being concentrated in six specialized centers generally recognized as being better equipped and more experienced in caring for them. In this study, the outcomes for patients seen in remote rural hospitals, larger community hospitals, and the more specialized centers were more or less the same, although the sophistication of the care needed and the expertise of those who gave it were greater at the specialized centers. There is little doubt but that the quality of neonatal care was improved overall, and it seems likely that the cost of the care may have been improved also, although this was not specifically addressed in this study.

There is good reason to think that both quality and cost of patient care can be improved. We no longer have unlimited resources, but it may be possible to use the funds and resources that are available more effectively and efficiently. It is likely that outcomes can be improved and costs reduced in situations where the advantages of scale can be achieved. This has been shown many times elsewhere in the American economy but has yet to be seriously applied in health care. There are, however, major centers where hearts or kidneys are transplanted and where quality is achieved by virtue of the volume of cases seen, with more or less attention to cost. There are other centers where there is high volume and good performance in the removal of cataracts, for instance, and where the incentive appears to be profit.

As the studies of Rosenblatt and others point out, there are economies of scale in medical care that can improve both quality and costs. It is true that these will often be at the expense of one-to-one personalization of care or easy geographic access to it. There is need for a balance between good personal or community care that is easily available and what might be called "high-tech" care, rendered in larger, less personal settings, where both quality and cost can be reflected in the economies of scale that can be more readily achieved in these intensive practice situations.

There is danger in all this. The specialized centers are inevitable and will increase in number for economic, technologic, and professional reasons. They will acquire concentrated experience and cumulative expertise and will, therefore, be able to render better technologic care to more patients, with better economic and quality control, than will be possible where there are fewer or perhaps only occasional patients with a given condition. But patient care has to be more than a mass production of technologic expertise for large numbers of patients. Patients are people and they need more than to receive transplanted organs or to have their cataracts removed. We must be certain that no serious division develops in patient care between the physician technicians, who do very specialized things in very specialized centers, and the more general physicians of any specialty who concern themselves with patients who seek help not only for diagnosis and treatment but in coping with their problem, whatever it may be. Somehow, we must avoid creating two distinct tiers of physician practice—primary care practitioners and technologic specialists—yet somehow, we must find ways to take better advantage of the beneficial effects that economies of scale can have on improving quality and reducing costs in patient care.

MSMW

Neurosyphilis

THE CENTERS FOR DISEASE CONTROL in January of this year noted that the incidence of secondary syphilis in 1987 was the highest since 1950, having increased 32% over the previous year.[1] As opposed to the recent past when the prevalence of syphilis was increasing in the promiscuous gay male population, the current increase was mainly in the heterosexual community. In the pre-penicillin era, neurosyphilis developed in a third of patients with primary or secondary syphilis. A similar percentage of inadequately treated or untreated patients would therefore be expected to have nervous system involvement in the antibiotic era. Acute syphilitic meningitis and meningovascular syphilis commonly occur in the first month following infection with syphilis and may be coincident with the rash of secondary syphilis.[2] Thus, symptomatic nervous system involvement may occur before patients recognize the disease or seek treatment. These are not uncommon problems; several cases of meningovascular syphilis are seen each year at the University of California, San Francisco, hospitals.

In view of the continued susceptibility of syphilis to penicillin therapy and the availability of sensitive serologic tests, the diagnosis and treatment of syphilis and neurosyphilis should be among the most straightforward in modern medicine. Regrettably, this is far from the case. The issues of the minimal diagnostic criteria for central nervous system syphilis, the interpretation of blood and spinal fluid serologic tests, the doses of antibiotics, and the assessment of their effects remain controversial. The review by Jordan elsewhere in this issue of the *Journal* is a scholarly, thorough, and timely synopsis of this complex literature.

Among the most controversial topics addressed by Jordan is the oft-stated opinion that normal spinal fluid—cells, protein, and serologic findings—does not exclude a diagnosis of neurosyphilis. As Jordan points out, the issue of normal spinal fluid in neurosyphilis is an inappropriate extrapolation from data in the early part of this century when the insensitive Wassermann test was used. In addition, these data were unreliable because of the erroneous inclusion of central nervous system diseases, such as carotid and vertebrobasilar stroke and viral meningitis—conditions that were undefined at that time. When such patients had abnormal serologic findings, they were included in these early series of neurosyphilis. It is now clear that syphilitic infection of the nervous system is the result of the most chronic, insidious, meningeal inflammatory process known: that induced by *Treponema pallidum*. The cerebrospinal fluid (CSF) will therefore reflect both the presence of the neurosyphilitic process and disease activity. A completely normal CSF essentially excludes neurosyphilis as the cause of a nervous system syndrome. This point has been repeatedly emphasized by Raymond Adams, Emeritus Professor of Neurology and Neuropathology at the Harvard Medical School.

Jordan further critiques the issue of "modern" criteria for the diagnosis of neurosyphilis and the issue of "modified" neurosyphilis. He pertinently notes that all such modified presentations of neurosyphilis were well described in the pre-antibiotic era. Accordingly, spinal fluid abnormalities and recognized clinical criteria make the diagnosis of neurosyphilis. There are no new or mysterious forms of the disease.

Penicillin remains the drug of choice for the treatment of syphilis and neurosyphilis. Central nervous system syphilis has developed following apparently successful intramuscular benzathine treatment of primary or secondary syphilis[3]; neurosyphilis should therefore be treated with intravenous penicillin. If one accepts that the adequate treatment of neurosyphilis is based on achieving treponemicidal levels of penicillin in the CSF, and that these levels are approximately 30 IU per liter or 0.02 mg per liter, then the correct dose of penicillin has been determined. Intravenous aqueous penicillin, in a dose of 0.15 million IU per kg of body weight in divided doses for 24 hours, will produce such concentrations.[4] The duration of adequate penicillin therapy is less clear since the spinal fluid abnormalities do not return fully to normal during 10 to 14 days (or even more) of high-dose intravenous penicillin therapy.[2] Again, the CSF is the indicator of adequate treatment. Follow-up CSF examinations will show a falling cell count and decreasing protein concentrations. The return of the CSF to normal finally establishes the eradication of the acute syphilitic process from the nervous system. This was the criterion proposed by Dattner in 1951.[5]

Jordan also addresses the recent proposal that concomitant infection with the human immunodeficiency virus (HIV) alters the course of neurosyphilis. The effect of altered cellular immunity from retroviral disease remains incompletely defined in regard to spirochetal infection. Jordan correctly points out that it is still highly speculative that syphilis is an opportunistic infection in patients with the acquired immunodeficiency syndrome (AIDS). The population data from south Florida do not support this contention.[6] Nor was neurosyphilis found as a frequent associated disease in the recent study of AIDS patients in Baltimore.[7]

Medical authors are often too quick to accept and uncritically repeat the statements of other authors. This tendency has led to unsubstantiated statements regarding the clinical features and the CSF findings of neurosyphilis and most recently concerning the alleged HIV attenuation of neurosyphilitic infection. Jordan's scholarly review brings a refreshing critical scrutiny to this vast and complex literature.

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Gastroesophageal Reflux—The Great Imitator

SYMPTOMATIC GASTROESOPHAGEAL REFLUX is an extremely common clinical problem. It has been estimated that approximately 10% of the population of the United States has daily heartburn requiring the regular use of antacids or other medications for symptom relief.[1] A much higher percent of the population, possibly more than 50%, has intermittent episodes of heartburn or "acid indigestion," often related to ingesting specific foods. Although heartburn is the "classic" symptom of gastroesophageal reflux, a great variety of other manifestations of chronic reflux have been recognized in recent times, as noted in the UCLA conference published in this issue of THE WESTERN JOURNAL OF MEDICINE.

The diverse manifestations of chronic gastroesophageal reflux can be particularly intriguing to clinicians and produce clinical syndromes of interest to many medical specialists. As our understanding of the complexities of chronic reflux has grown, it has been evident that the term "gastroesophageal reflux disease" provides a more appropriate umbrella under which the varying manifestations of this disorder can be included. Under this diagnostic category, one can readily place patients with typical heartburn (with or without objective esophagitis); patients with silent reflux presenting with a complication of chronic reflux, such as a peptic stricture in Barrett's esophagus; or patients with one of the many symptoms of the pharynx, larynx, or respiratory tract. These are not new concepts. Otolaryngologists have been aware for many years that hoarseness secondary to posterior laryngitis (the so-called Cherry-Donner syndrome) might be a manifestation of gastroesophageal reflux disease.[2] Likewise, allergists and chest physicians have long suspected that some bronchospastic conditions, particularly "nonallergic" or "intrinsic" asthma, might be precipitated by gastroesophageal reflux.[3] Other manifestations of the disease include recurring substernal chest pain that may mimic cardiac disease and various unusual symptoms such as chronic hiccough, loss of dental enamel, and even dyspareunia.

In accepting the potential for gastroesophageal reflux to produce chronic pharyngitis, laryngitis, or pulmonary problems, a critical question is, how common are these clinical conditions? Our recent experience with 24-hour intraesophageal pH monitoring has indicated that as many as 75% of patients with chronic hoarseness will show an abnormal amount of gastroesophageal reflux.[4] It has recently been suggested that 45% to 65% of adults with asthma will have reflux.[5] It is difficult to be certain about the actual frequency of these relationships because a specific diagnosis of abnormal reflux has not been easy to obtain. Many prior studies linking gastroesophageal reflux disease to these clinical syndromes have relied on diagnostic indicators—hiatal hernia on x-ray film, "typical" symptoms of heartburn—that are not very reliable. Even more specific techniques to establish its presence, such as identifying definite esophagitis by endoscopy, have been restricted because many patients with extraesophageal manifestations of reflux may not have esophagitis. The development of reliable and practical techniques for ambulatory prolonged recording of intraesophageal pH has allowed more precise identification of the

potential relationship between abnormal amounts of gastroesophageal reflux and these clinical syndromes. Studies of this kind have revealed that many patients with chronic hoarseness or intermittent bronchospasm will have abnormal reflux patterns, often in the absence of esophagitis. One has to be somewhat cautious, however, in accepting the excessive acid exposure in the distal esophagus as proof of causation for these extraesophageal manifestations. In the case of bronchospastic symptoms, this dilemma is compounded by the knowledge that bronchodilating drugs, such as theophylline, can produce decreases in lower esophageal sphincter pressure. Thus, the abnormal reflux in these patients could be a result of a patient's therapy, rather than a cause of the patient's symptom. With these reservations, in our large experience with 24-hour pH monitoring, we have come to regard both chronic hoarseness and intermittent bronchospasm as indications for using this diagnostic test. In the case of intermittent bronchospasm, we feel that the test becomes a greater diagnostic aid if a patient's intermittent symptoms can be shown to be regularly associated with a decrease in the intraesophageal pH to less than 4.0 during testing. Preliminary observations with a "double probe" pH recording technique have been only somewhat helpful. In these studies, with a second probe placed in the upper esophagus or in the hypopharynx, only occasionally have patients been shown to have recorded acid exposure in these more proximal locations. It is hoped that future studies will provide even better techniques for monitoring acid exposure in the hypopharynx.

There have been some attempts to document actual aspiration of gastric contents in patients with unexplained chronic pulmonary difficulties. By the use of radioisotopic tagging of gastric contents, aspiration may conceivably be documented during subsequent scanning of the chest.[6] These studies have often been done with technetium Tc 99m because the absorbed isotope is secreted by the gastric parietal cell, thus providing a constant source of isotope tag in the gastric secretions. Unfortunately, the isotope is also secreted by the salivary glands, raising the question whether aspirate containing the isotope truly represents gastric contents.

Treatment of gastroesophageal reflux disease and its many manifestations has received considerable attention in recent years. This has resulted in a clear improvement in the therapeutic approach to these patients. It is interesting that most therapies seem to be primarily directed at suppressing the acid content, implying that the disease is primarily due to abnormal acid secretion. Studies into this possibility, however, have proved that this is not the case. Patients with chronic esophagitis have usually been shown to have normal amounts of acid secretion. A more likely hypothesis is that gastroesophageal reflux is primarily a motility disorder, produced by inadequate closing pressures of the lower esophageal sphincter or ineffective peristaltic clearing pressures in the distal esophagus.[7] This is supported by observations that patients with primary peristaltic and sphincter failure, such as those with esophageal scleroderma, frequently have severe reflux abnormalities and that peristaltic and sphincter pressures are more likely to be abnormally low in patients with the most severe or complicated disease. Thus, the various manifestations of gastroesophageal reflux disease are not due to too much acid but to acid in the wrong place. Neutralizing or inhibiting the gastric acid content remains the backbone of effective reflux therapy, however, and the development of more effective and longer-acting acid inhibitory drugs promises to provide more effective treatment for these patients. It is important that we not forget the simpler approaches to reflux, particularly convincing patients to sleep with the head of the bed elevated. Because long periods of acid reflux frequently occur at night in these patients, this aspect of the treatment regimen remains important. Studies with intraesophageal pH monitoring have documented that elevating the head of the bed on 15-cm (6-in) blocks will significantly decrease the total overnight acid exposure time in these patients.[8] Finally, increasing attention is being directed toward the development of drugs that might enhance the abnormal motility present in these patients—so-called prokinetic, or promotility, drugs. Additive therapy with bethanechol chloride or metoclopramide hydrochloride should definitely be considered a part of the therapy in these patients when effective acid suppression has not adequately controlled the symptoms. Newer prokinetic drugs, such as domperidone and cisapride, promise to enhance our ability to effectively treat these patients. A surgical approach to a case that is truly refractory to appropriate medical therapy is warranted, and fundoplication can often offer relief for these patients.

Although the many clinical manifestations of gastroesophageal reflux disease have been known or suspected for many years, the development of improved diagnostic techniques, particularly ambulatory 24-hour pH monitoring, has provided the opportunity for a clearer understanding of these relationships. Reflux is a common event and produces symptoms that involve many specialties. It should be carefully sought when symptoms suggestive of this abnormality are present. In a questionable situation where this diagnosis seems a reasonable possibility, a six- to eight-week trial of good antireflux therapy should be considered as a diagnostic and therapeutic venture.

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Case Reports

Coccidioidomycotic Brain Abscess in an HIV-Infected Man

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PRIMARY COCCIDIOIDOMYCOSIS is a pulmonary infection caused by the soil fungus *Coccidioides immitis.* "[When] primary pulmonary infection fails to heal, either chronic pulmonary lesions, or dissemination supervenes. . . . Dissemination via the bloodstream occurs in 0.1% of Caucasians, and in up to . . . 10% of Filipinos and Orientals."[1] While more than a dozen cases of disseminated infection have been reported in patients with the acquired immunodeficiency syndrome (AIDS),[2-10] there has not been a description of a brain abscess due to *C immitis.* We report a fatal case of disseminated coccidioidomycosis in a homosexual man with AIDS-related complex who during life had a focal lesion in the brain stem localized by magnetic resonance (MR) imaging that at autopsy proved to be a brain abscess containing *C immitis* sporangia, spherules, and hyphae.

Report of a Case

The patient, a 26-year-old sexually active gay man, had a history of prostatitis and chronic perianal problems including candidiasis, rectal condylomata, and herpes simplex. He presented with myalgias, arthralgias, fatigue, a low-grade fever of 37 to 38°C (99 to 100°F), and a slightly productive cough and was given a course of trimethoprim/sulfamethoxazole that transiently reduced his symptoms.

Within six weeks of his initial presentation, the patient again was seen complaining of fatigue, with abdominal cramping and diarrhea. Two of two stool specimens contained *Giardia lamblia* cysts. Treatment was begun with the administration of quinacrine hydrochloride, followed by metronidazole hydrochloride, resulting in the resolution of his diarrhea and nausea. Subsequent stool cultures and multiple evaluations for parasites were negative. Despite normalization of his temperature over the next several weeks, his fatigue continued and he reported occasional night sweats. At that time, a chemistry panel, thyroxine level, and urinalysis were normal, and tests for hepatitis B surface antigen and antibody and a rapid plasma reagin test were negative. His leukocyte count was 7,800 per μl with 22% lymphocytes.

Five months after his initial presentation, the patient began having daily morning headaches and nightly temperature elevations to 38°C (101°F). Examination at this time revealed palpable, rubbery supraclavicular nodes and an 8-kg (18-lb) weight loss.

His chest x-ray film showed a right-sided mediastinal prominence. A computed tomographic (CT) scan of the chest confirmed the presence of a right and left paratracheal adenopathy and mild splenomegaly. Blood cultures were negative, the erythrocyte sedimentation rate (Westergren) was 90 mm per hour, and an arterial blood gas determination with the patient breathing room air showed a partial oxygen pressure of 81 torr and a partial carbon dioxide pressure of 33 torr. Repeated complete blood cell counts, quantitative immunoglobulin G analysis, cryptococcal antigen titers, cytomegalovirus (CMV) titers, barium enema, sigmoidoscopy, and bronchoscopy with transbronchial biopsies were all normal. A bone marrow biopsy specimen showed nonspecific hyperplasia. The T-cell helper/suppressor ratio was low at 0.1 (normal 0.9 to 3.5). An initial complement fixation serologic test for *Coccidioides immitis* was positive at a titer of 1:128. The patient refused a superficial lymph node biopsy.

The patient's daily headaches gradually increased, requiring oral and intravenously given narcotic analgesics. A CT scan of the head showed a discrete 4-mm midbrain lesion without evidence of a mass effect (Figure 1). No other abnormality was seen. A lumbar puncture was done and showed a normal opening pressure, normal protein and glucose contents, a cell count consisting of two monocytes, and normal india ink and acid-fast bacilli (AFB) stains. There was no growth on cerebrospinal fluid cultures for bacteria, AFB, CMV, or fungi. Because the patient refused treatment with amphotericin B, he was started on a regimen of oral ketoconazole, 400 mg daily, which resulted in the resolution of his fever. Repeat complement fixation titers for *Coccidioides* at one and three months after the initial 1:128 titer were greater than 1:512. Human immunodeficiency virus (HIV) antigen was detected in his serum at this time.

An MR scan of the head showed a single, high-signal focus in the right midbrain substantia nigra. It measured 5 mm in diameter and was heterogeneous with indistinct margins. There was also a mild increase in the size of the sulci, indicating some brain volume loss (Figure 2).

He was observed for five months further while receiving oral ketoconazole and increasingly stronger doses of narcotics daily for severe, generalized headaches. The condition of the patient remained unchanged, without the development of nuchal rigidity or increased peripheral adenopathy. A low-grade fever was well documented in the range of 37.8 to 38.3°C (100 to 101°F). Further spinal fluid evaluation was refused by the patient, and intrathecal antifungal therapy was not initiated.

The patient was admitted to hospital 16 months after his initial presentation for rehydration and control of pain and nausea. On the morning of his death, he was noted to be confused, with a right-sided coarse tremor and athetosis. The right pupil was enlarged to a diameter of 6 mm with the left pupil 3 mm in diameter. Respirations and pulse rate were regular. He was found by the nursing staff to be unresponsive.

(Jarvik JG, Hesselink JR, Wiley C, et al: Coccidioidomycotic brain abscess in an HIV-infected man. West J Med 1988 Jul; 149:83-86)

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ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
CNS = central nervous system
CT = computed tomography/ic
HIV = human immunodeficiency virus
MR = magnetic resonance

Neuropathology

The patient's corpse was refrigerated, and an autopsy was done 28 hours postmortem. The brain weighed 1,700 grams and showed diffuse cerebral edema. The meninges appeared opacified and thickened, most prominently at the base of the brain, where there was softening of the brain stem and cerebellar cortices. The cerebral hemispheres were symmetric and without evidence of herniation. Coronal sectioning revealed smooth ventricles of normal caliber. There was no gross evidence of infarction, hemorrhage, or other focal lesion, except for a minute parenchymal cavitation in the right midbrain.

Microscopic sections from the meninges at the base of the brain showed abundant sporangia and spherules of *C immitis* with acute and chronic inflammation, focal necrosis, and focal granulomatous inflammatory reaction. The fungal organisms included characteristic spherules containing endospores and abundant immature spherules. Occasional spherules were identified within multinucleated giant cells (Figure 3). One focus of hyphal elements was noted, including some focal, barrel-shaped arthrospores characteristic of *Coccidioides* hyphae, which were admixed with immature spherule forms (Figure 4). There were perivascular chronic inflammation and focal necrosis of the brain-stem parenchyma (pons) adjacent to areas of meningeal infection.

Sections from the minute cavitary lesion in the right midbrain showed an abscess, 5 mm in diameter, containing spherules of *C immitis,* with focal necrosis of parenchyma and chronic inflammatory reaction.

Sections from the brain stem showed focal microglial nodules, some of which contained large cells with eosinophilic intranuclear inclusions consistent with cytomegalovirus. No spongiform change or multinucleated giant cells suggestive of HIV were identified.

Discussion

Coccidioides immitis is a dimorphic fungus that is endemic to the arid regions of the southwestern United States, Mexico, and Central and South America. After the arthrospores are inhaled, cell-mediated immunity restricts the infection to the lung and prevents dissemination.[1]

Because patients with AIDS have severely compromised cell-mediated immunity, they are at high risk for disseminated fungal infections. Levy and co-workers reviewed 315 cases of AIDS patients with central nervous system (CNS) involvement.[2] Although the most common infection was toxoplasmosis (103 cases), *Cryptococcus neoformans* was the most frequent fungal infection (41 cases). They reported only one case of coccidioidomycosis. In a second series, Anders and colleagues found CMV to be the most frequent CNS infection (14.4%), followed by *Toxoplasma* (13.4%), with *Cryptococcus* again being the most common fungal infection (8.7%) and no cases of CNS *C immitis.*[11]

To date there have been fewer than 20 reported cases of coccidioidomycosis in AIDS patients. None of the individual reports of disseminated coccidioidomycosis in AIDS patients[3-9] described CNS involvement. The case of disseminated coccidioidomycosis in the series of Levy and associates had *C immitis* meningitis with microabscesses containing spherules throughout the cerebellum found at autopsy.[2] Most recently, Bronnimann and co-workers reported seven cases of coccidioidomycosis in AIDS patients, one of whom had spherules found in the brain stem.[10]

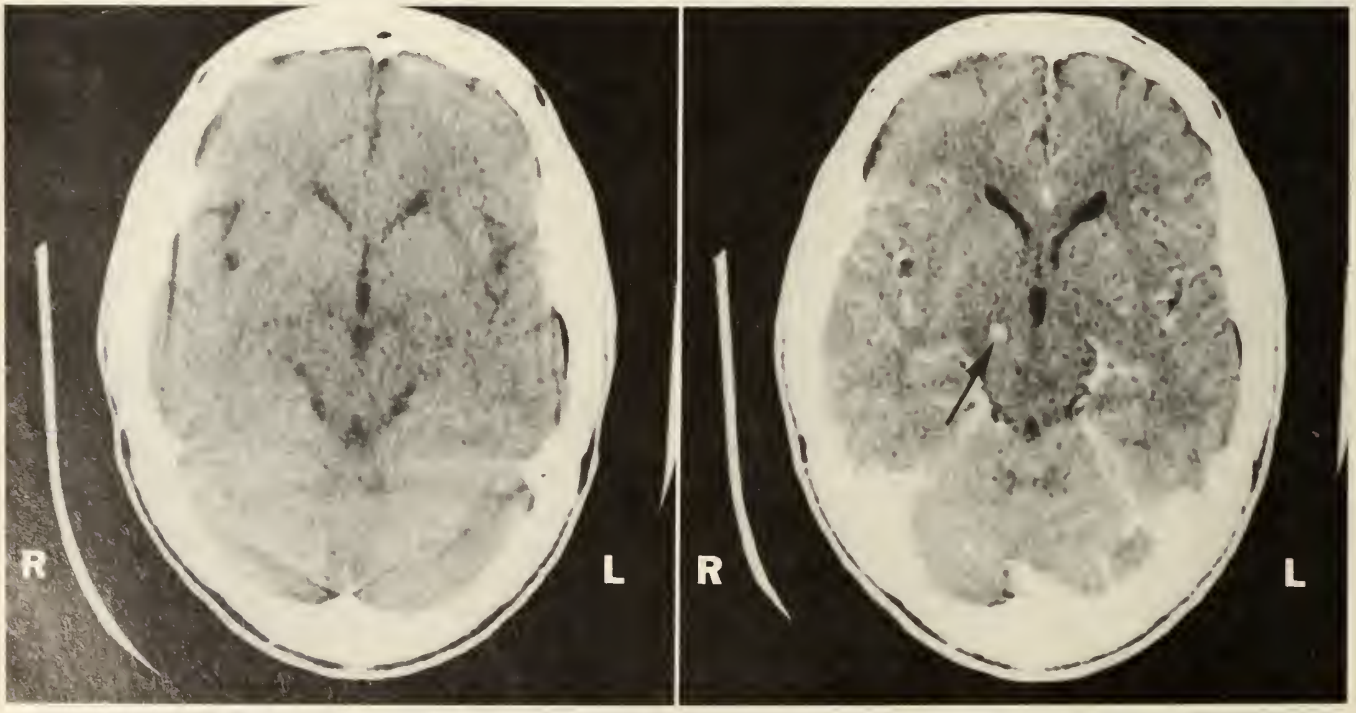

Figure 1.—Plain **(left)** and contrast-enhanced **(right)** computed tomographic scans show a discrete 4-mm midbrain lesion **(arrow)** that enhances with contrast.

The spectrum of lesions reported for *C immitis* meningitis includes leptomeningitis, cerebritis, infarcts, and, less commonly, miliary granulomata.[12] A CT scan usually shows ventricular dilatation indicating a noncommunicating hydrocephalus, but it may also show cisternal obliteration, cisternal enhancement, ependymal enhancement, and hypodense white matter lesions, presumably due to vasculitis and subsequent infarction.[13]

The MR scan on our patient showed a single, 5-mm midbrain lesion with distinct margins and a low-signal center, without evidence of ventricular enlargement. Although magnetic resonance has been shown to be more sensitive,[14] its specificity is still about equal to that of computed tomography.[15] In our patient there is nothing specific about the lesion's appearance to distinguish it from other focal infectious processes or tumor.

The pathogenesis of the *C immitis* abscess is probably similar to that of abscesses caused by other fungal infections. The most likely scenario is that the meninges were hematogenously seeded by a focus outside of the CNS, in this case from the lungs, and subsequently the fungus spread deep into the midbrain through the cerebrospinal fluid by following the Virchow-Robin space.

Conclusions

C immitis brain abscess must now be added to the long list of complications that can occur in patients infected with HIV. Although coccidioidomycosis is still relatively uncommon among AIDS patients and CNS infection by *C immitis* is even rarer, the rapidly accumulating case reports[2-10] suggest that *C immitis* will be an increasingly important pathogen. Moreover, as the incidence of AIDS increases in the Ohio and Mississippi river valleys, the frequency of disseminated *Histoplasma capsulatum* infection, which has already been well documented,[16-19] will undoubtedly also increase. Whereas complement fixing antibody testing may be helpful in diagnosing *C immitis* infection in immunocompromised patients, serology cannot precisely diagnose specific CNS lesions. This is a particularly important point in AIDS patients because they are likely to have multiple infec-

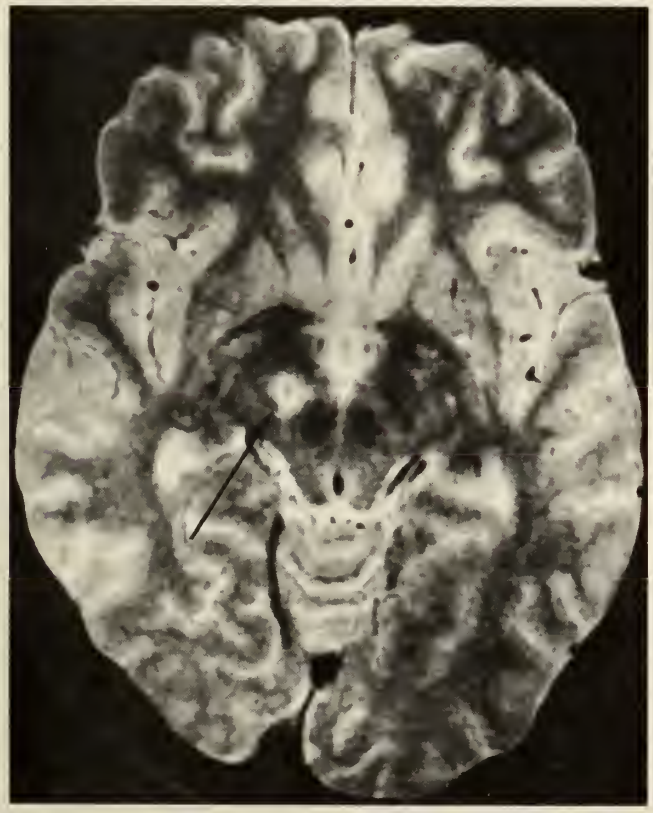

Figure 2.—A magnetic resonance scan (TR 2,000 ms, TE 70 ms) shows a heterogeneous, 5 mm in diameter, high-signal focus **(arrow)** with indistinct margins in the right midbrain. There is also a mild increase in the size of the sulci, indicating some brain volume loss.

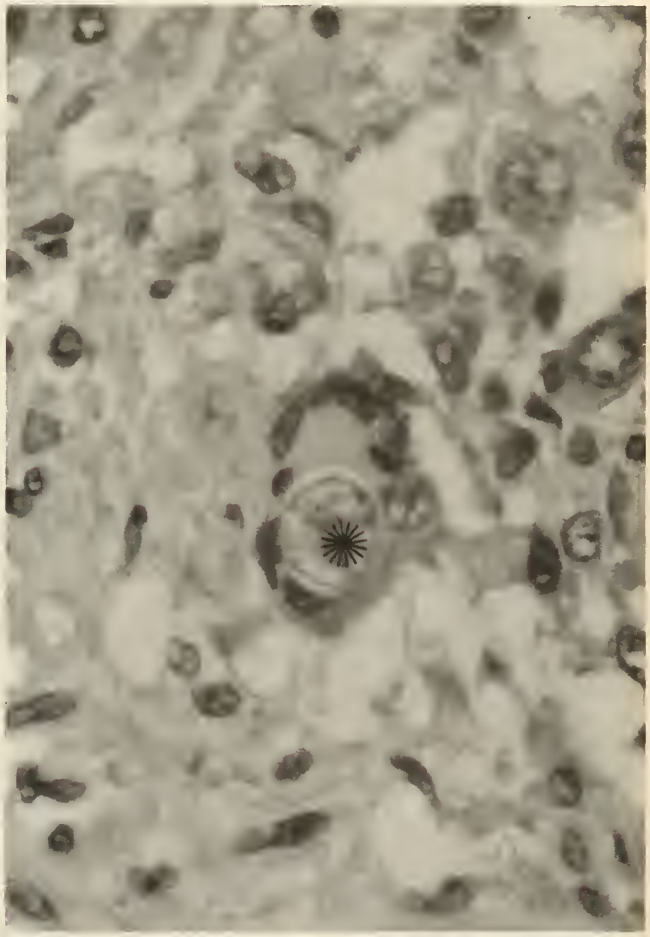

Figure 3.—A hematoxylin and eosin-stained paraffin section from the midbrain shows a *Coccidioides* spherule **(asterisk)** within a multinucleated giant cell (original magnification × 200).

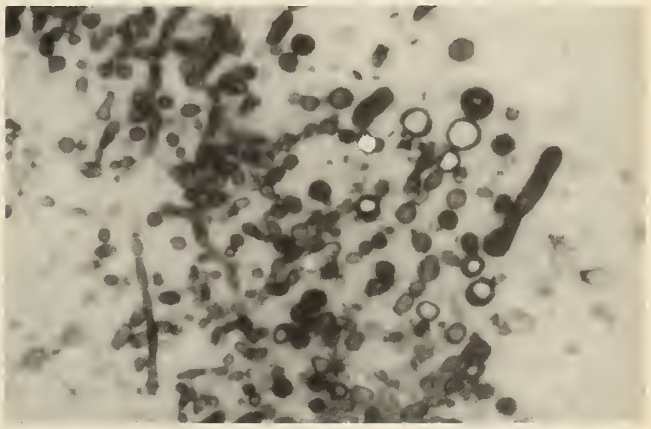

Figure 4.—A silver methenamine-stained paraffin section of the midbrain shows barrel-shaped arthrospores characteristic of *Coccidioides immitis* hyphae admixed with immature spherule forms (original magnification × 200).

tious and neoplastic processes. Unfortunately, neither CT nor MR is sufficiently specific for the precise diagnosis of the various possible brain lesions in AIDS. Because early appropriate therapy is of paramount importance in the immunosuppressed, our description of a CNS mass lesion due to *C immitis* emphasizes the importance of doing a biopsy of an accessible brain lesion in a patient with AIDS.

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Congestive Heart Failure and Sudden Death in a Young Woman With Thyrotoxicosis

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THE EXISTENCE OF "hyperthyroid heart disease" with resultant congestive heart failure has been a matter of controversy for a number of years. Some clinicians feel that thyrotoxicosis merely overstresses a heart with valvular, coronary, or other preexisting organic disease.[1] Other clinicians have reported congestive heart failure in patients in whom a careful search failed to reveal any other cause of heart disease and that resolved when the patients' thyrotoxicosis was treated.[1-11] Few postmortem evaluations of hearts of patients with presumed thyrotoxic congestive heart failure have been done to definitively confirm the absence of other significant disease. The death of this young thyrotoxic patient, who had congestive heart failure in the absence of atrial fibrillation, provided an opportunity to do anatomic, histologic, and biochemical evaluations of human myocardial tissue in this syndrome.

Methods

Clinical Testing

Thyroid function tests during the patient's early course were done at Consolidated Medical Laboratories, Highland Park, Illinois. Clinical tests during her final month were done at Michael Reese Hospital and Medical Center, Chicago. Thyroid-stimulating hormone (TSH) levels were determined using the Gammadab Kit (Travenol-Genetec Diagnostics, Cambridge, Mass).

Electron Microscopy of Myocardial Tissue

Myocardial tissue was taken at autopsy about 19 hours after death. Tissue for electron microscopy was fixed in 2.5% glutaraldehyde, postfixed in osmium tetroxide, dehydrated in graded alcohols, and embedded in epon. Sections were stained with uranyl acetate and lead citrate and were examined in a Philips 300 electron microscope.

Biochemical Characterization of Cardiac Myosin

Ventricular myosin was prepared as described by Offer and co-workers[12] with slight modifications used by Lompre and associates.[13] Myosin was prepared from this patient and from three human hearts from patients without thyrotoxicosis to serve as controls. The control patients had no history of heart disease, were not taking cardiac drugs, and their hearts had no evidence of significant disease. Myosin isotype composition was evaluated by a solution phase radioimmunoassay analysis using a monoclonal antibody to V3 cardiac myosin, as previously described.[14] Purified rat V1 and V3 isomyosins served as control standards. Rat V3 isomyosin was iodinated with sodium iodide I 125 by the lactoperoxidase procedure, and each myosin was evaluated for its ability to compete for antibody binding relative to the labeled rat V3. Logit transforms of combined data from two to four competition curves of each specimen were evaluated by linear regression analysis.

Results

Report of a Case

This 34-year-old woman had been generally well until January 1984, when she began having tremulousness, ner-

(Magner JA, Clark W, Allenby P: Congestive heart failure and sudden death in a young woman with thyrotoxicosis. West J Med 1988 Jul; 149:86-91)

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ABBREVIATIONS USED IN TEXT

AV = atrioventricular
SSKI = saturated solution of potassium iodide
T_3 = triiodothyronine
T_4 = thyroxine
TSH = thyroid-stimulating hormone

vousness, heat intolerance, and diffuse headache. There was no history of heart disease. A small goiter was noted, but there was no ophthalmopathy, and hyperthyroidism was diagnosed. Treatment was begun with propylthiouracil, 50 mg given three times a day, and she felt better, but in March 1985, icterus, nausea, vomiting, and weight loss developed, and she had as many as eight bowel movements per day. Gallstones were not detected, and a liver biopsy specimen showed minimal nonspecific changes without eosinophils. The thyroid uptake of radioiodine was 59% at 24 hours, and 8 mCi of sodium iodide I 131 was administered. Giving methimazole worsened a rash present on the legs, so metoprolol tartrate and propylthiouracil, 50 mg three times a day, were prescribed.

Three months later she complained of heat intolerance and tremulousness. The thyroxine (T_4) level was 4.8 μg per dl, triiodothyronine (T_3) resin uptake 26%, and a T_3 level by radioimmunoassay was 590 ng per dl. Because the liver function test results had recently been abnormal, the propylthiouracil therapy was discontinued. During the next few weeks her tremulousness and nervousness worsened. In December 1985, a thyroid scan disclosed diffuse bilateral enlargement. The thyroid uptake of radioiodine was 55% at 6 hours and 34% at 24 hours. A dose of 28 mCi of ^{131}I was administered, and a week later a saturated solution of potassium iodide (SSKI), eight drops per day, was prescribed.

Two months later the patient had tachycardia and was tremulous. The T_4 level was 19.2 μg per dl, the T_3 resin uptake 40%, and the T_3 level by radioimmunoassay exceeded the upper limit of the test range of 800 ng per dl. The regimen of SSKI and metoprolol was continued, but she remained clinically and biochemically thyrotoxic.

The patient was then seen at the Michael Reese Endocrinology Clinic for evaluation. She complained of nervousness, tremulousness, and palpitations and had discontinued taking the SSKI and metoprolol a few days before coming to the clinic. She was thin, weighing 45 kg (100 lb), her blood pressure was 140/80 mm of mercury, and pulse 120 per minute and regular. There was no ophthalmopathy. The extraocular muscle movements were intact, as were the visual fields. The thyroid was firm and diffusely enlarged, with the right lobe measuring 7 by 4.5 cm and the left lobe 5.5 by 4 cm. The chest was clear, and the cardiac and abdominal examinations elicited no abnormalities. A pronounced tremor of the hands was present. The possibility of a TSH-producing pituitary adenoma was considered. Therapy with propranolol hydrochloride, 20 mg three times a day, was prescribed. A random TSH value was 1.5 μU per ml, which was barely detectable in the assay.

Two weeks later the patient felt generally improved. The tremulousness and palpitations had resolved, but she complained of nervousness, abdominal cramps, nausea, and right upper quadrant pain. Her pulse was 76 per minute and regular. She had minimal hand tremor. A coned-down x-ray film of the sella turcica was normal. A thyrotropin-releasing hormone test was done to detect a possible inappropriate elevation of TSH. The TSH levels at 0, 15, 20, and 30 minutes were 1.2, 0.9, 1.1, and 1.0 μU per ml, respectively. The T_4 value was 28 μg per dl, the T_3 resin uptake 52%, and a T_3 level by radioimmunoassay 671 ng per dl. It was concluded that the patient had Graves' disease rather than a TSH-producing tumor. Therapy with propranolol, 20 mg three times a day, was continued, and arrangements were made to admit the patient to an isolation room so that a large dose of ^{131}I could be administered.

Two weeks later the patient was admitted for pretherapy evaluation. She had no complaints of tremulousness or palpitations, but had chronic, dull, right upper quadrant pain. She was afebrile, her blood pressure was 140/80 mm of mercury, pulse rate was 80 per minute and regular, and respirations were 20 per minute. On examination, the head and thyroid were unchanged. Examination of the chest disclosed dullness at the right base to percussion and auscultation without rales. On cardiac examination, the point of maximal impulse was dynamic and was displaced laterally 2 cm in the fifth intercostal space. There was a grade II/VI holosystolic murmur at the apex radiating to the axilla and a murmur at the left lower sternal border that was unchanged with respirations. The jugular venous pulse had prominent ventricular waves and was elevated 10 cm. The abdomen was flat, soft, and nontender, with normal bowel sounds. There was trace pedal edema.

The hematocrit was 35%, leukocyte count was 6,000 per μl with a normal differential, and the platelet count was normal. The serum sodium, chloride, bicarbonate, urea nitrogen, creatinine, and creatine kinase levels were normal. The serum potassium value was 3.5 mEq per liter. The total bilirubin level was 1.2 mg per dl, and alkaline phosphatase 337 normalized units per dl (normal 25 to 100). The serum aspartate and alanine aminotransferase levels were normal. The urine was yellow, cloudy, and had a specific gravity of 1.012, a pH of 5, 1+ protein, 4+ occult blood, 4 erythrocytes per high power field, and a few squamous cells. Moderate cardiomegaly was present on a chest x-ray film. There was a right pleural effusion and a small left pleural effusion. The lung fields were clear, and the pulmonary vasculature was normal. The electrocardiogram showed a sinus rhythm, a rate of 69, accelerated atrioventricular (AV) conduction, and repolarization changes consistent with left ventricular hypertrophy.

Combined M-mode and two-dimensional echocardiographic studies showed the left atrium to be moderately dilated to 3.8 cm, 2.7 cm per m^2 (normal < 2.2 cm per m^2). The left ventricular chamber was also slightly increased in size. The right ventricular and right atrial chambers were severely dilated, and there was paradoxic septal wall motion. The overall left ventricular contraction was diffusely hypokinetic. All valves appeared to be normal. A pattern consistent with pulmonary hypertension with loss of the a wave was noted, however. A Doppler study detected mild mitral regurgitation, severe tricuspid regurgitation, and pulmonic regurgitation consistent with pulmonary hypertension. A bubble study showed persistence of bubbles compatible with tricuspid regurgitation. There was no evidence of an atrial septal defect or a right-to-left shunt. The mitral valve excursion was 14 mm and intraventricular septal thickness 9 mm. The posterior wall thickness was 8 mm and excursion 10 mm. The left

ventricular chamber diameter was 5.3 cm in diastole and 4.3 cm in systole.

In view of her somewhat low serum potassium level, a single oral dose of 40 mEq of potassium chloride was administered in anticipation of diuretic therapy. She was in a private room for the anticipated ^{131}I therapy, and a few minutes after the potassium was administered, she was discovered to be in full cardiac arrest and was not successfully resuscitated.

Necropsy Findings

The thyroid was enlarged, weighing 73.7 grams. Sections showed a largely involuted, diffuse hyperplasia (Figure 1) and no evidence of thyroiditis. Her thymus was large for her age, weighing 47.2 grams. Other than a few B-lymphocyte aggregates, without germinal center formation, it showed a normal architecture. The heart weighed 295 grams and showed dilatation of all chambers, more prominent on the right. There was pronounced left ventricular endocardial fibroelastosis. No valvular lesion or evidence of coronary artery disease was seen. Light microscopy revealed varying myocardial cell size, hyperlobated nuclei, focal severe interstitial fibrosis, and scattered round cell infiltrates (Figure 2). On electron microscopy there was a mild increase in variably sized mitochondria (Figure 3). There were also scattered electron-dense granules seen within mitochondria. Cristal architecture could not be assessed accurately due to postmortem autolysis.

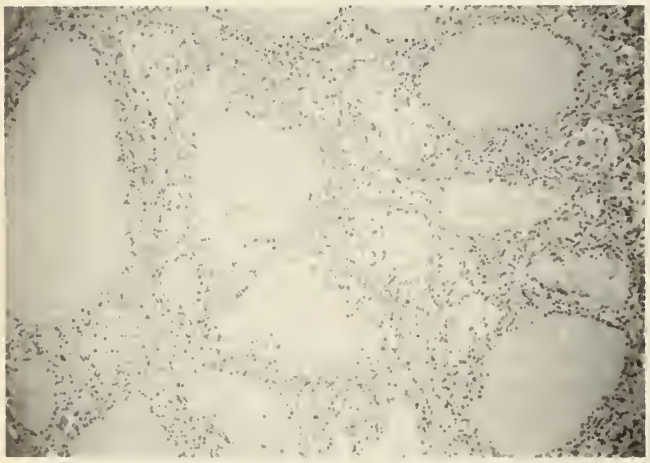

Figure 1.—The photomicrograph shows the histologic appearance of the thyroid. There was a generally involuted, diffuse hyperplasia and no evidence of thyroiditis (hematoxylin and eosin, original magnification × 110).

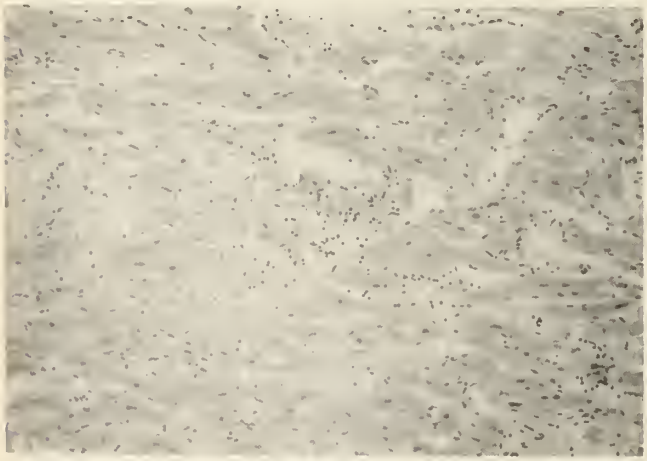

Figure 2.—The photomicrograph shows the histologic appearance of the heart. Myocardial cells varied in size and had hyperlobated nuclei. There were focal severe interstitial fibrosis and scattered round cell infiltrates (hematoxylin and eosin, original magnification × 140).

Biochemical Characterization of Cardiac Myosin

Myosin was prepared from myocardial tissue from this patient and from three human hearts from nonthyrotoxic patients to determine whether the proportions of V1 and V3 myosin isotypes were altered by thyrotoxicosis. Myosin isotype composition was evaluated by radioimmunoassay using a monoclonal antibody to V3 cardiac myosin. The results (Figure 4) do not indicate any detectable difference in myosin isotypes in the thyrotoxic patient compared with the controls.

Discussion

Cardiac function has long been known to be altered in patients with thyrotoxicosis. In 1825 Parry described the cases of eight patients with exophthalmos and goiters who also had palpitations, irregularity of the pulse, edema, and cardiac enlargement.[15] Some clinicians maintained that thyrotoxicosis alone could cause heart disease,[1-11] while others thought that associated heart disease, such as coronary artery disease, was always present in such patients in addition to thyrotoxicosis.[1] This question was addressed by Sandler and Wilson in 1959.[1] Of their 462 patients with thyrotoxicosis, 150 had evidence of cardiac dysfunction—auricular fibrilla-

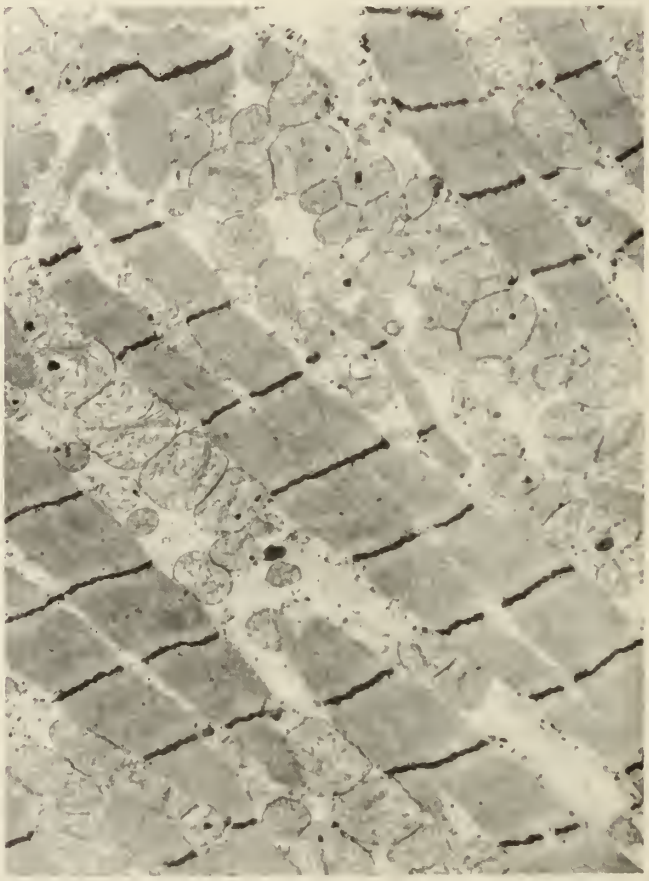

Figure 3.—On electron microscopy of the myocardium, the mitochondria were mildly increased in number, and some contained electron-dense granules (original magnification × 15,732).

tion, congestive heart failure, cardiomegaly, or all three. Of these 150 patients, 64 (43%) had no clinical, radiologic, or electrocardiographic evidence of any associated heart disease. Neither the duration nor the severity of thyrotoxicosis appeared to be relevant factors in producing cardiac complications in these 64 patients. Of particular relevance to the present case, of the 26 patients with congestive heart failure in this group, 23 also had auricular fibrillation that was thought to be a significant contributing factor. Thus, our case was similar to only three described by these workers in which the patients had sinus rhythm, congestive heart failure, but no evidence of associated cardiac disease. More recently there have been several reports of a reversible cardiomyopathy in thyrotoxicosis,[8,9] especially in children.[11] The untimely death of our patient provided a unique opportunity to anatomically document the absence of unsuspected organic heart disease in a patient with presumed "thyrotoxic heart disease" and to do histologic and biochemical analyses of the myocardial tissue.

Tachycardia and a bounding precordium are typical clinical signs in cases of thyrotoxicosis. In addition to its increased rate, the heart manifests an increased stroke volume, cardiac output, and pulse pressure, and the circulation time is decreased.[16] Cardiac blood flow and myocardial oxygen consumption are increased, and the velocity of contraction is shortened.[17] Experimentally induced thyrotoxicosis in animals causes a change in the pattern of myosin isoenzymes, but this has not been reported in humans.[18-26] Thyroxine greatly increases the number of mitochondria in heart muscle cells.[27,28] Myocardial hypertrophy has been described both in animals given thyroid hormones[23,29-31] and in humans with hyperthyroidism.[32,33]

Formerly it was thought that thyroid hormones mediated these effects on the myocardium by the action of catecholamines on the adenylate cyclase system. Levey and Epstein

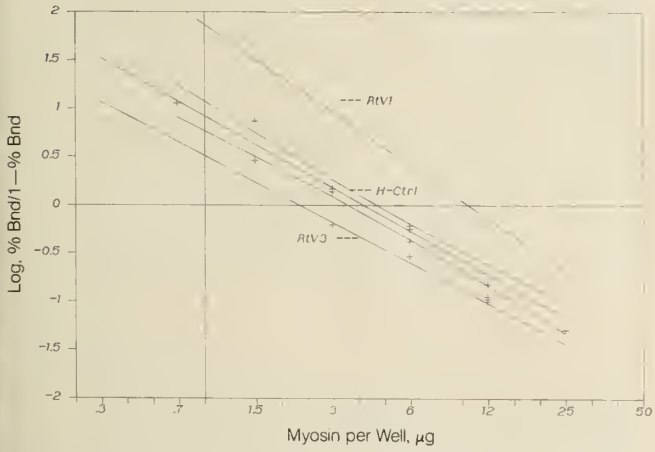

Figure 4.—The graph shows the results of radioimmunoassay analysis of human thyrotoxic myosin. Increasing amounts of standard rat V1 myosin **(top line)**, myosin prepared from control human myocardium **(center line)**, and of standard rat V3 myosin **(lowest line)** were used to compete for binding of rat V3 labeled with iodine 125 with a monoclonal antibody to rat V3. For clarity, data points for the three regression lines have been omitted, and curves representing the 95% confidence limits are shown for the control human myosin only; the confidence limits for the other lines were comparable. The data points (+) for incubations using myosin prepared from the thyrotoxic patient's myocardium are plotted. There was no difference in the competitive binding of thyrotoxic myosin to monoclonal V3 antibody compared with control human myosin.

proposed, however, that there are separate adenylate cyclase systems for thyroid hormones and catecholamines,[34] and this topic has been addressed in a recent review.[35] It is now accepted that in hyperthyroidism myocardial tissue has a normal sensitivity to catecholamines, and plasma catecholamine levels are not increased. In isolated cat papillary muscle, the level of thyroid hormone greatly affects the intrinsic contractile state, independent of noradrenaline stores and alterations in high-energy phosphates. Thyroid hormones may also alter the intracellular handling of calcium by myocardial cells.[33]

Although thyroid hormones generally have positive inotropic and chronotropic effects, unexplained congestive heart failure without dysrhythmia has occasionally been reported, as noted above. Several studies have indicated that mild pulmonary hypertension exists in thyrotoxic patients.[36,37] Bishop and colleagues found that the work of the right ventricle was increased, in part due to the increased blood volume and more rapid venous return.[37] Tricuspid regurgitation is often seen in severe right ventricular failure and is believed to be due to right ventricular dilatation rather than to primary valvular disease. Dougherty and Craige reported two cases of apathetic hyperthyroidism in elderly patients that presented as tricuspid regurgitation and severe congestive heart failure.[5] Characteristic jugular venous pulse tracings with exaggerated C and V waves and steep y descent were documented. Both patients responded dramatically to treatment of their thyrotoxicosis. Associated organic heart disease was believed to be mild, but this was not proved histologically.

An autopsy examination in the present case disclosed that the heart was dilated with left ventricular endocardial fibroelastosis, which suggested a chronic congestive cardiomyopathy. The fibroelastosis was extensive and may have compromised ventricular function in this patient; it is not clear whether the fibroelastosis represented an independent pathologic process or was related to the hyperthyroidism. There was no evidence that the compromised cardiac function resulted from ischemic, hypertensive, valvular, or congenital heart disease. Our patient did not abuse drugs or alcohol, and there was no evidence to suggest cardiomyopathy due to viral infection, amyloidosis, hemochromatosis, sarcoidosis, connective tissue disease, neuromuscular disease, neoplasia, glycogen storage disease, or lipoidosis.

Previous reports of myocardial histologic findings in hyperthyroidism were summarized by Saphir[38] and included nonspecific findings, such as histiocytic, lymphocytic, and fibroblastic cellular accumulations; edema and necrosis; swollen fibers with indistinct striations and lipoid changes; hyalin replacement of muscle fibers; myocardial hypertrophy; and, in some cases, no changes. Ultrastructurally, increased numbers, size, and complexity of mitochondria have been reported in animals after thyroxine administration[27,39]; our observation of dense granules associated with cristae is of uncertain significance and may represent a postmortem change. The findings in our case of a focal interstitial fibrosis with a mild round cell infiltrate and increased numbers of mitochondria, although nonspecific, are consistent with some of these observations.

A biochemical analysis of myosin isotypes present in human myocardial tissue from a patient with thyrotoxicosis has not previously been published. In rats and rabbits, administering thyroid hormone in high doses causes the V1

isoform to increase relative to the V3 isoform.[18-26] Several methods have been devised for estimating cardiac myosin isoforms: adenosine triphosphatase-specific enzyme activity of purified myosin; mobility of native myosin isoforms on pyrophosphate, nondenaturing gels; and immunologic analysis. Comparison of these methods by others has shown that none could give a totally reliable estimate of the exact isomyosin composition in humans. Mercadier and co-workers reported that normal fetal and adult human myocardium contains both V1 and V3 isoforms but that the predominant isoform is of the V3 type,[25] as was also shown by Clark and associates.[14] Mercadier found that the maximum proportion of V1 expressed in the normal population was about 15%. Their study used an affinity purified polyclonal anti-V1 antibody rather than monoclonal anti-V3 as used in our study. Although use of an anti-V1 probe provides greater sensitivity for detecting the V1 isotype, the V3 antibody used here would have been able to detect the expression of the V1 isotype had it exceeded 25%. This level of V1 expression was not observed in the thyrotoxic tissue. This result is not an artifact of autolysis during the 19-hour period after the patient's death because intact myosin was extracted from the tissue, and the monoclonal antibody used will recognize denatured and trypsinized V3 isomyosin.

In view of the autopsy findings, our patient is thought to have died of a sudden ventricular arrhythmia. Although atrial fibrillation may occur in about 20% of patients with thyrotoxicosis, other cardiac arrhythmias are uncommon, and sudden death has rarely been reported. Atrial fibrillation was found in 207 of 1,000 cases of thyrotoxicosis reported by Ernstene[40] and in 84 of 462 cases reported by Sandler and Wilson.[1] Less common dysrhythmias and conduction disturbances[41,42] were atrial flutter, first- and second-degree AV block, third-degree AV block, reversible bundle branch block, ventricular ectopic beats, ventricular tachycardia, and ventricular fibrillation.

In 1923 Bickel described two cases of sudden death in patients with hyperthyroidism that he attributed to ventricular fibrillation.[43] In 1945 Boone described the case of a 37-year-old woman with hyperthyroidism who had electrocardiographic proof of a period of ventricular fibrillation; because she recovered, no anatomic proof of the absence of other heart disease was obtained.[44] Lyngborg and Jacobsen reported the case of a 59-year-old man with thyrotoxicosis who died of intractable ventricular tachycardia,[45] and they comment that theirs is the first such case of thyroid hormone-induced fatal ventricular tachycardia to have been reported. Of note, their patient had mild diabetes mellitus and hypertension and was admitted to hospital following a posterior wall myocardial infarction two weeks before his death, so coronary artery disease and acute myocardial ischemia likely played important roles in the genesis of his arrhythmia. Parker and Lawson published a series of 33 patients who died primarily of thyrotoxicosis.[46] Factors that indicated a poor prognosis included tachycardia (greater than 120 beats per minute), atrial fibrillation, congestive heart failure, and thyroid crisis. Of these patients, 18% had a major embolism and 61% (20 patients) had congestive heart failure. Five patients (15%), however, died suddenly and unexpectedly, and necropsy showed no evidence of a myocardial infarction or pulmonary embolus. Thus, the sudden death of our young patient must be viewed as an extremely unusual event.

In conclusion, we were unable to document other organic heart disease in a young patient with cardiomyopathy thought to be due to thyrotoxicosis. Despite the poor myocardial function clinically, a normal V3 isotype of myosin predominated in this patient, unlike the situation in some thyrotoxic animal model systems in which the V1 isotype increases. Factors other than an altered myosin isotype may contribute to poor myocardial function in some humans with thyrotoxicosis.

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Irreversible Interstitial Pneumonitis Associated With Tocainide Therapy

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THE ADMINISTRATION OF several chemotherapeutic, antibiotic, and antiarrhythmic agents has been associated with the development of an interstitial pneumonitis indistinguishable histologically from the idiopathic form.[1,2] Previous case reports have described an alveolitis caused by tocainide therapy.[3,5] In each case, the pulmonary changes were responsive to cessation of the drug therapy and administering corticosteroids. We report a case of an acute interstitial pneumonitis developing in a patient receiving tocainide that was rapidly and irreversibly progressive, resulting in death despite discontinuing the use of the drug and promptly initiating steroid therapy.

Report of a Case

The patient, an 80-year-old man, had myocardial infarction complicated by congestive heart failure in October 1985. After the infarction his resting left ventricular ejection fraction was determined to be 21% by gated wall motion radionuclide study. Before discharge, a chest x-ray film showed cardiomegaly and findings consistent with mild residual congestive heart failure without evidence of intrinsic pulmonary disease (Figure 1). In February 1986, he presented to our hospital because of increasing shortness of breath and cough for three days before admission. He said he did not have associated coryza or hemoptysis. On admission he had a blood pressure of 108/80 mm of mercury, a heart rate of 90 beats per minute, respirations of 24 to 28, and a temperature of 38.7°C (101.6°F). Examination of the lungs revealed bilateral rales. His chest x-ray film showed extensive bilateral interstitial infiltrates (Figure 2). Blood gas determinations made with the patient breathing room air showed a pH of 7.54, partial oxygen pressure of 63 torr, oxygen saturation 94%, and partial pressure of carbon dioxide 32 torr. His medication regimen at admission was the following: nifedipine (Procardia), 10 mg three times a day; furosemide (Lasix), 40 mg a day; digoxin, 0.25 mg a day; nitroglycerin (Transderm-Nitro); captopril, 25 mg three times a day; and tocainide, 400 mg three times a day. Tocainide therapy had been started for recurrent nonsustained ventricular tachycardia three months before he was admitted.

During the patient's hospital admission, administration

Figure 1.—The October 1985 chest x-ray film shows cardiomegaly without evidence of intrinsic pulmonary disease.

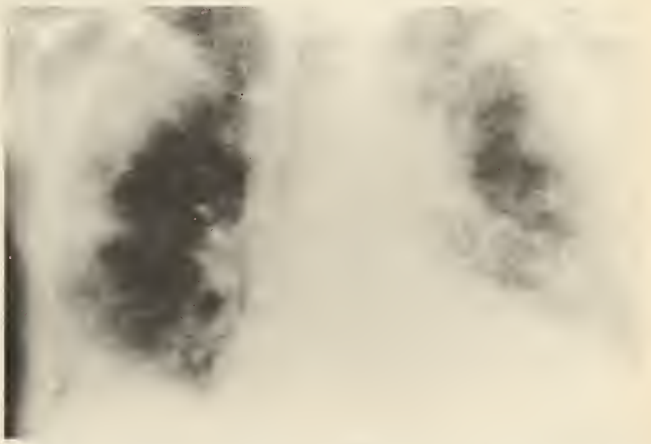

Figure 2.—A chest x-ray film on admission shows extensive interstitial infiltrates with relative sparing of the perihilar region.

(VanNatta B, Lazarus M, Li C: Irreversible interstitial pneumonitis associated with tocainide therapy. West J Med 1988 Jul; 149:91-92)

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of the tocainide was stopped and prednisone therapy at 60 mg a day was promptly initiated. The patient's pulmonary state continued to deteriorate, however, and he required intubation and the administration of positive end-expiratory pressure. On the ninth day of hospital stay, acute right-sided chest pain developed. A chest x-ray film showed a 45% to 50% pneumothorax, and a chest tube was placed. The patient's pulmonary state continued to worsen, and he died the following day. An autopsy was done, and microscopic examination of the lungs revealed an organizing interstitial pneumonitis characterized by proliferating intra-alveolar fibrotic tissue. Focal areas of normal lung parenchyma were also noted.

Discussion

Tocainide, an analogue of lidocaine, was first marketed in the United States in November of 1984. It has been shown to be equivalent to conventional agents in suppressing premature ventricular ectopy and malignant ventricular tachyarrhythmias. Common adverse reactions to the use of tocainide include central nervous system manifestations (dizziness, tremor, mental confusion, ataxia, and paresthesias) and gastrointestinal complaints (nausea and vomiting). These symptoms will occur in a significant proportion of patients during initial dose adjustments.[3] Hepatitis, agranulocytosis, aplastic anemia, and encephalopathy have been reported in a small number of cases. Worsening of congestive heart failure is unusual with oral therapy.[3]

The first report of pulmonary complications resulting from the use of tocainide appeared in 1980.[3] In a patient treated for ventricular arrhythmia, interstitial pulmonary edema developed that persisted despite diuretic therapy. A lung biopsy specimen showed interstitial pneumonitis. The tocainide therapy was stopped and corticosteroid therapy begun; afterwards pulmonary function and chest x-ray film findings improved.

In 1981, increasing dyspnea developed in two patients at two and six months, respectively, after the initiation of tocainide therapy.[4] Chest x-ray films showed increased interstitial markings, and pulmonary function tests revealed hypoxia and a decreased diffusion capacity. A lung biopsy specimen in one patient showed interstitial fibrosis. Administration of the drug was discontinued in both patients and prednisone was administered in one. Two weeks later, pulmonary function test results were much improved and the infiltrates had cleared. Both patients showed substantial clinical improvement.

A fourth case of tocainide-induced interstitial pneumonitis was reported in 1982.[5] The patient had been taking the drug for two months before symptoms developed. Abnormal chest x-ray films, pulmonary function studies, gallium scan, and clinical findings showed improvement one week after the use of tocainide was stopped and prednisone therapy was started.

Our patient's clinical and radiologic presentation is not unlike that of the previous reports. Discontinuing the use of tocainide and administering steroids were not, however, associated with reversal of pulmonary dysfunction. The patient continued to have an abnormal chest roentgenogram and showed continued deterioration of pulmonary function requiring intubation. At autopsy, histopathologic changes were still present. To our knowledge, this is the first reported case of an irreversible pulmonary fibrosis related to tocainide administration.

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Correspondence

Piroxicam and Doxepin in Pain Management

To THE EDITOR: I read with a great deal of interest the article about piroxicam and doxepin by Cohn and co-workers in the March issue.[1]

Many of us in oncologic practice are familiar with the efficacy of nonsteroidal anti-inflammatory agents as well as tricyclic antidepressant therapy for relief of cancer pain. These authors, however, point out that 17 of the 30 patients treated with the regimen of piroxicam and doxepin ultimately required supplemental narcotics for adequate pain control and 6 patients abandoned therapy altogether because of severe side effects. Thus, their regimen was at least no better and perhaps worse than narcotic analgesics in 23 out of their 30 patients or 76% of their trial group. In addition, a notorious error in the design of pain management trials is the omission of a placebo control group, which was also lacking here.

I think therefore that the authors can hardly be justified in their conclusion that therapy with piroxicam and doxepin was both safe and efficacious.

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Parallels

To THE EDITOR: In a recent editorial you wondered "if the time has not come for frustrated and sometimes angry physicians . . . to be born again, to use a contemporary term, in a personal renewal of their original commitment to medicine."[1]

I could not agree more, although I am curious to know your definition of "contemporary." The phrase "born again" was first used nearly 2,000 years ago by Jesus of Nazareth in speaking to Nicodemus, as recorded in John 3:3.

In fact, as I reread this chapter, I see some parallels between Nicodemus and the physicians you were writing about. Nicodemus was a scholar, a teacher, and a man respected in his community. He was frustrated and confused because he did not understand some of the things going on around him. His scholarly instincts told him where to go for answers, and modern physicians would do well to consult the same source.

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REFERENCE

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Cocaine-Associated Rhabdomyolysis

To THE EDITOR: I enjoyed reading the excellent article, "Acute Renal Failure Due to Rhabdomyolysis Associated With Cocaine Toxicity," by Lombard and co-workers in the April issue.[1] The authors attribute the rhabdomyolysis to sympathetic overactivity with resultant vasoconstriction and microinfarctions with skeletal muscle necrosis. The possibility of seizure activity and multiple ecchymosis could not be excluded as a cause of rhabdomyolysis.

In a recent article, Menasche and Gottlieb reported the case of a 35-year-old man who developed hyperthermia, rhabdomyolysis, and myoglobinuric renal failure after the recreational use of cocaine.[2] The patient had a small bruise over the left eye but no other evidence of trauma. Seizure, fasciculations, tremor, and muscle rigidity were not seen. These authors suggest that cocaine administration may lead to increased body temperature both by resetting of hypothalamic heat regulating centers and by vasoconstriction, resulting in diminished peripheral heat loss. The use of cocaine during the summer months or in areas with high ambient temperature and humidity is particularly dangerous, as this may further prevent dissipation of body heat. The resulting hyperthermia may lead to a clinical situation similar to that of a heat stroke, with rhabdomyolysis and myoglobinuric renal failure.

Menasche and Gottlieb's report suggests that cocaine administration may by itself cause rhabdomyolysis without seizure activity and multiple ecchymosis. More case reports are necessary before this interesting phenomenon can be elucidated.

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Safe Needles

To THE EDITOR: Practicing medicine today demands special vigilance with needles because of the possibility of accidental infection with hepatitis and the acquired immunodeficiency syndrome. Needle accidents may occur when health care personnel try to re-cap needles and accidentally stick themselves. Needle cutters do not work well with the fine-gauge needles used in the practice of allergy. Large red plastic containers are available for the deposit of needles and syringes, but our staff has found the containers too bulky for counter space use and too awkward when reaching down to the floor with an exposed syringe and needle in order to pass them through the small mouth of the container. Patients were concerned when they observed an open canister of used needles. Also, there are times when it is preferable to re-cap needles.

Looking for a solution to the problem, I punctured a hole slightly smaller than a needle cap into the top of a soup tin can and placed the can in a drawer. The hole in the can serves as a prop for the needle cap. My intent was to create a safe method that requires only one hand to re-cap a needle and frees the other hand. To reinforce this approach, staff deliberately stand with one hand behind the back while reinserting the needle into the cap suspended by the can. The disarmed needle and syringe are then safely discarded. I suggest that an extra cap be initially left in the support. After that cap is

safely attached to a needle and syringe, the next one is inserted in the hole for the subsequent needle. In this manner there is always a receptor cap in place for the next needle. Because caps are tapered, the hole size is not critical.

In situations where no drawer or fixture is available, we have placed a few ounces of modeling clay on the work surface and used the same safety measures. The clay, with the cap supported in an indentation, serves the same function as the perforated can.

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Oat Bran

To the Editor: We have discovered a reporting error in our article, "Oat Bran as a Cholesterol-Reducing Dietary Adjunct in a Young, Healthy Population," in the March issue.[1] The grams per day dose of oat bran listed on the last line of Table 5 (page 301) and in the first sentence of the last paragraph (page 302) should be 34 instead of 17. This change does not otherwise alter the data or study conclusions.

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Cerebral Blood Circulation and Brain Death

To the Editor: There is a neglected, far quicker, cheaper, and easier way to conclude whether or not cerebral blood circulation exists than the complex nuclear imaging procedure advocated by Drs Braunstein and Wang in the April issue.[1] All one needs is an ophthalmoscope, some tap water, and a patient without ocular cataracts.[2,3]

It is important to keep the cornea moist with a drop or two of water every 20 to 30 seconds. If circulation is stagnant, retinal arteries may be absent or very narrow. Retinal veins may be intact, but usually the venous columns are broken into clean or somewhat sludgy segments of various lengths—the so-called box car effect. The segments may be stationary or slowly moving. The movement may last only a few seconds or for several minutes, and I postulate that the interval of movement corresponds to the period of time available for resuscitation without clinical sequelae (variable for every person).[2]

If arteries and veins are intact without segmentation, active circulation can be verified by applying light fingertip pressure on the eyeball during ophthalmoscopy. The result is striking: blanched vessels with sharp pulses of blood coincident with heartbeats, traversing the arteries over the rim of the optic disc. I saw this in a stuporous patient on whom no pulse or blood pressure could be detected—counting each spurt of blood in unison with a running electrocardiogram monitored by another observer.

Such findings in one eye should be convincing evidence of the status of cerebral circulation; in both eyes, this is almost certain evidence. Here is one area where a "high-tech" approach would seem to be ostentatious and wasteful frippery, except perhaps for cases of prohibitive ocular pathology.

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Correction

To the Editor: I would like to note a correction needed in my epitome in the May issue.[1] As it is printed, a sentence reverses my meaning. It should read, "Detection of bronchiectasis by CT scan, though still somewhat controversial, is clearly more reliable and convincing with high-resolution scans." I would like to emphasize that high-resolution computed tomography (CT) is superior to conventional CT for bronchial as well as parenchymal detail.

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Topics in Primary Care Medicine

Screening Mammography

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Breast cancer is the most commonly occurring cancer in women and, until recently surpassed by lung cancer, was the leading cause of cancer-related death in women. It is the leading cause of death in women aged 39 to 44 years. The American Cancer Society has estimated that there will be 135,000 new cases of breast cancer and 42,300 breast cancer-related deaths in 1988. It is now predicted that breast cancer will develop in one out of every ten women in the United States. Given the clinical and public health significance of breast cancer, annual screening with mammography and clinical breast examination is recommended for women aged 50 and older to reduce breast cancer mortality.

"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

The incidence of breast cancer in the United States is one of the highest in the world, and it is increasing, particularly in women younger than 40 years. Various factors have been proposed to explain changes in the breast cancer incidence, including changes in childbearing patterns, diet, the hormonal milieu, and increased detection. While epidemiologic studies have identified risk factors for breast cancer, the disease is so common that all women should be considered at risk. The American Cancer Society estimates that 75% of breast cancers will occur in women without known risk factors.

In the absence of dramatic improvements in survival for a given breast cancer stage and lacking methods that might prevent the disease, attention has been directed toward the early detection of breast cancer with the intent of finding curable disease and improving survival. Though many factors, including age, menopausal status, hormone receptor status, tumor histology, and cellular kinetics, are important determinants of survival, the tumor stage at diagnosis is the most widely used and perhaps the most important prognostic factor at this time. Because the tumor stage at diagnosis is an important determinant of survival and randomized clinical trials have shown that mortality from breast cancer can be reduced with screening, the early detection of breast cancer by aggressive screening has been recommended. The methods of screening include breast self-examination, clinical breast examination, and mammography. While the evidence concerning the effectiveness of breast self-examination in screening is mixed, there is strong evidence for the effectiveness of clinical breast examination and mammography in detecting earlier stages of breast cancer and reducing mortality. Because the recommendations regarding mammography have been somewhat controversial and its use much less than recommended, this discussion will focus on the use of mammography in screening asymptomatic women for breast cancer.

The attributes of a good screening test include high sensitivity, high specificity, good patient and physician acceptance, low risk, and relative cost-effectiveness. A disease suitable for screening must have certain characteristics. These include a relatively prevalent detectable preclinical phase, serious consequences, and, an important factor, the disease must have a treatment that is more effective when applied to screening-detected disease than when applied to symptom-detected disease. An effective screening test should improve either survival, the quality of life, or both.

Several studies regarding the effectiveness of mammography as a screening test have shown that mammography prolongs survival and reduces the mortality from breast cancer. The first randomized clinical trial of mammography was the Health Insurance Plan of Greater New York (HIP) study, which in 1964 enrolled 62,000 women aged 40 to 64. At ten years of follow-up, this study showed a 30% reduction in breast cancer mortality among the study group of 32,000 women offered screening with an annual mammogram and clinical breast examination over four consecutive years, as compared with controls who continued to receive their usual medical care. At 14 years of follow-up (10 years after the last screening), the reduction in breast cancer mortality was 20% (118 deaths versus 153). These findings are even more remarkable given that they reflect the mortality reduction of the entire group *offered* screening, of which only two thirds ever

(Humphrey LL, Ballard DJ: Screening mammography. West J Med 1988 Jul; 149:95-97)

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ABBREVIATIONS USED IN TEXT

ACP = American College of Physicians
BCDDP = Breast Cancer Detection Demonstration Project
HIP = Health Insurance Plan [of Greater New York Study]

participated in the study. Both clinical breast examination and mammography independently contributed cases not detected by the other. Of the breast cancers detected in the screened women, a third were detected by mammography only, and 79% of cases detected by mammography only had normal axillary nodes at a surgical procedure. In the control group, 48% of the cases had normal axillary nodes at the operation. The screening benefit was initially thought to be primarily in women between ages 50 and 59, but subsequent HIP analyses have shown that the reduction in mortality extends to screened women in all enrolled age groups (40 to 64 years).

A more recent Swedish randomized trial of single-view mammography alone every 24 to 33 months in 163,000 women aged 40 to 74 showed a 31% decrease in mortality in the population offered screening (acceptance 89%) as compared with controls receiving their usual medical care. In the age group 50 to 74, the decrease in mortality was 40%. The screened population had a 25% reduction in stage II and in more advanced breast cancer. After year 7, this study showed a reduced mortality in the 40- to 49-year age group. These results are similar to those from the HIP study.

The Breast Cancer Detection Demonstration Project (BCDDP) was a voluntary screening program involving more than 280,000 women aged 35 to 74 years. Though the study lacked a control group, it showed a substantial decrease in the stage of breast cancer at diagnosis when mammography and clinical breast examination were combined. In this study, mammography detected 95% and clinical breast examination 33% of all breast cancers. Mammography alone detected 42% of all breast cancers, of which a third were found in women between ages 40 and 49. Furthermore, 70% of all screening-detected cases had normal axillary nodes. The BCDDP showed five- and ten-year relative survival rates of 88% and 79%, respectively, in the 4,240 women with histologically confirmed breast cancer. This improvement in overall survival and in survival in various disease subcategories was also seen in women diagnosed with breast cancer before age 50.

Two case-control studies from the Netherlands also have confirmed the effectiveness of mammography in screening for breast cancer. The Nijmegan study, involving 30,000 women who received single-view mammography alone every two years, showed a mortality reduction of 50% in the screened versus the unscreened population. This risk reduction extended to all age groups. The Utrecht project enrolled 14,796 women aged 50 to 64 and evaluated clinical breast examination and mammography. Using an age-matched control group, the risk of dying from breast cancer in those screened was 70% less than in those never screened.

Several other studies have shown the effectiveness of mammography in detecting early breast cancer and reducing mortality. Studies in which only single-view mammography was used as a preliminary screen or in which the screening interval was 24 to 33 months have shown a reduced mortality in the screened women. Its effectiveness has also been established in women younger than 50 years. Therefore, there is substantial evidence supporting the use of mammography as a screening procedure.

While studies show that mammography is effective, it is also important to understand the limitations of the test and the clinical implication of these limitations. Due to variations in technology and the distribution of disease in screened populations, the reported sensitivity of mammography ranges from 60% to 94% and the specificity from 88% to 99%. The predictive value will vary with the prevalence or prior probability of the disease and sensitivity and specificity of the test. In the screening setting, the positive predictive value of mammography ranges from 10% to 35% and the negative predictive value generally is greater than 95%. The clinical significance of these statistics is that for each breast cancer diagnosed by mammography, there will be a number of false-positives that also require evaluation. The number of false-positive tests will vary with the prevalence of breast cancer—that is, as women age, the prevalence of breast cancer increases and the proportion of false-positive tests decreases. Similarly, when the prior probability of disease is high, the proportion of false-positive tests decreases. The ratio of biopsies with malignant to those with benign results from screening referrals ranges from 1:9.3 to 1:1.1, with a mean of 1 cancer detected per 3 biopsies. Because the sensitivity of the test is between 70% and 90% and the negative predictive value less than 100%, it must be emphasized that a normal mammogram does not rule out breast cancer and any clinically suggestive finding requires a timely evaluation. Also, symptomatic women younger than 45 have a higher rate of false-negative tests, possibly attributable to the increased breast glandularity of premenopausal women.

Even with these acknowledged limitations, early detection of breast cancer is possible and effective in reducing mortality. Therefore, annual screening with mammography and clinical breast examination for women older than 50 has been recommended. The age at which to begin mammography, however, has been controversial. Because BCDDP found that a third of the detected breast cancer cases occurred between ages 35 and 49 and were primarily diagnosed by mammography, the American Cancer Society and American College of Radiology recommend that screening begin with a baseline mammogram between ages 35 and 40 and that annual or biennial mammography begin at age 40. The American College of Physicians (ACP), citing concerns of possible radiation risk, personal and financial costs, lack of evidence, and concern about the high rate of false-positive tests, has not concluded that screening of asymptomatic women in this age group is warranted. When risk factors are present, they feel the benefit of screening "probably outweighs any potential harm." For women aged 60 to 69 years, the ACP reserves recommendations for screening to individual clinical judgment.

Despite evidence supporting the use of mammography, national data on its use in women older than 50 suggest that only 17% to 41% of women have had a mammogram at some time in their life and that only 4% to 15% of women in this age group receive mammography annually. When women are asked why they do not avail themselves of mammography, a high proportion respond that their physicians do not recommend it to them. A recent survey of physicians in Los Angeles found that only 11% of respondents followed American Cancer Society mammography guidelines. A survey of 509 family physicians in the state of New York found that most

believed mammography to be an effective procedure for detecting breast cancer in its early stages but that only 8% recommended an annual mammogram for asymptomatic women older than 50 years. The major deterrents to its use were concern about its safety and reliability, the low probability of detecting breast cancer with screening, patient acceptance, and cost.

Determining the cost of mammography is complex and involves considering a wide range of factors. The direct cost of mammography ranges between $25 and $150, depending on the type of mammogram, the number of views taken, and regional variations in health care costs. There is a growing trend among radiologists to provide mammography screening at reduced prices, which should substantially affect the cost-benefit ratio. In most cities in the US, mammography is now available for less than $50. Physicians who have avoided referring women for mammography because of its high cost should seek out radiology practices that provide quality mammography at reduced prices. Furthermore, as more women are referred for mammography, the cost per examination should be reduced.

In addition to the direct cost of mammography, there are also many hidden financial and personal costs. These include the cost and risk of follow-up of positive tests and the anxiety created among those with false-positive tests. Recommendations for biopsy vary among medical centers, with an average ratio of malignancy per biopsy in the US of 1:3. While this represents a substantial addition to the overall cost of screening, recent evidence suggests that there is useful prognostic information to be gained from "benign" biopsies. It is generally agreed that women with proliferative benign breast disease have an increased risk of breast cancer, and recent histopathologic studies have found that subcategories of women with pathologically confirmed benign breast disease are at a substantially increased risk of breast cancer. Another risk with screening mammography is that patients or physicians may be falsely reassured by false-negative tests and delay evaluating suggestive lesions. Also, there is some concern that with the increasing use of mammography, physicians and other health care providers may become less skilled and less diligent in their clinical breast examination. It must be stressed that the clinical examination and mammography are complementary procedures and that a normal mammogram does not rule out breast cancer, as its negative predictive value significantly varies with the probability of disease.

Physicians and women also are appropriately concerned about the small but finite risk of radiation exposure. While no level of radiation is without risk, the levels of radiation required for modern mammography range from 0.2 to 0.4 rad (midplane breast view). Extrapolations from high-dose radiation exposure data suggest that radiation-induced breast cancer would develop after a 10- to 20-year latency period in 1 to 8 women per year among 1 million women screened with a single midplane breast view giving a mean dose of 0.2 to 1.0 rad. This risk is much less than many of the normal risks associated with daily living. Recent evidence also has shown that the risk of breast cancer associated with radiation exposure diminishes with age and is primarily focused in women younger than 30 years.

In summary, several studies have shown that screening mammography with clinical breast examination is effective in diagnosing early breast cancer and in decreasing mortality from breast cancer. It is recommended annually for women 50 years and older by almost all organizations, and evidence exists that it is also effective in reducing mortality in the 40- to 49-year age group. Mammography is underused in the US for several reasons, of which cost and concern about radiation exposure are most often cited by women and physicians. These concerns must be assessed in the context of a disease that will affect 10% of women during their lifetime and for which diagnosis and treatment at an early stage are the most significant determinants of survival. It is important that physicians understand the significant benefits and also the limitations of screening for breast cancer with clinical breast examination and mammography. Further research must be directed towards determining the optimal timing, frequency, and interval of mammography and breast examination in women of varying risk to enable the design of feasible and effective breast cancer screening programs. A large clinical trial of screening for breast cancer is currently underway in Canada. This study will further define the role of clinical breast examinations and mammography in women ages 40 to 59 and will assess whether combinations of risk factors identify subsets of women with different screening requirements.

Though consideration of a formal cost-benefit analysis with respect to mammography is outside the scope of this review, when this method of analysis was applied to the HIP study, the cost per person-year saved was estimated to be less than $4,000 and the overall net effect of the screening procedure was estimated to be a gain of nearly $1.5 million. Mammography is one of the most cost-effective preventive measures available to primary care physicians.

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Health Care Delivery

Outcomes of Regionalized Perinatal Care in Washington State

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We evaluated the extent to which the regionalization of perinatal care in Washington State has succeeded in concentrating high-risk pregnancies in technologically appropriate referral centers and in reducing differences in neonatal outcome among hospitals. Of all infants weighing less than 1,500 grams born between 1980 and 1983, nearly 68% were delivered in level III hospitals, although only 24% of all babies are born in these hospitals, indicating that the state is highly regionalized. Neonatal outcomes—as measured by standardized mortality ratios—are similar in level I, II, and III hospitals and are not greatly influenced by the rural or urban location of the hospital. The most promising strategy for further reducing neonatal mortality is to decrease the number and proportion of very-low-birth-weight births.

(Rosenblatt RA, Mayfield JA, Hart LG, et al: Outcomes of regionalized perinatal care in Washington State. West J Med 1988 Jul; 149:98-102)

Neonatal mortality has declined dramatically in the United States over the past 20 years.[1,2] A major factor contributing to this improvement in infant survival is more effective perinatal technology, particularly in the care of low-birth-weight infants.[3-6] Regionalization of perinatal care has been widely adopted as a strategy to bring high-risk mothers and babies to specialized perinatal centers to reduce regional differences in the availability of sophisticated perinatal care. A major intent of regionalizing perinatal care is to minimize differences in outcome attributable to the geographic location.[2,7-10]

Regionalizing perinatal care is of particular importance in a state like Washington with a large rural population. Washington State has more than 30 small hospitals located in rural counties and only 6 tertiary perinatal centers. In recent years, a statewide system of perinatal regionalization has evolved, with four regional perinatal subsystems covering most areas of the state. This study evaluates the extent to which Washington State's regionalized perinatal care system has been successful in concentrating high-risk pregnancies in technologically appropriate referral centers, reducing disparities in neonatal outcome among hospitals of different types, and eliminating differences that may be attributable to maternal locale.

Methods

From 1980 to 1983, 90 hospitals in Washington State routinely offered obstetric services. Of all births in the state, 96% occurred in these hospitals, with the remainder in free-standing birthing centers, physicians' offices, hospitals that did not routinely provide obstetric care, in transit to the hospital, or at home. During this four-year period, 264,618 births and 1,571 neonatal deaths—deaths of live-born infants between 0 and 27 days of age—were recorded in the 90 hospitals studied.

Level of Care Classification

As part of the process of regionalizing, every hospital offering obstetric and neonatal care is assigned to one of the mutually exclusive categories of care, ranging from level I for uncomplicated obstetric and neonatal care to level III for tertiary care requiring sophisticated obstetric and neonatal capabilities. The difference between one level and the next is at times indistinct, and, with the exception of level III nurseries, the state does not formally categorize hospitals. To categorize the level of care available in Washington State obstetric hospitals, we conducted telephone interviews with hospital staff to ascertain the presence of relevant equipment (such as respirators), personnel (such as in-house anesthetists or anesthesiologists, neonatologists), and services (such as genetic counseling, short-term versus long-term respiratory support). Based on this information, Washington's hospitals were assigned to level I, II, or III according to guidelines published by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists.[11] All six level III facilities currently recognized by the state conformed to the published criteria and were assigned level III status. The 11 hospitals classified by our telephone survey as level II had varied levels of respiratory support available, but all had in-house anesthetists or anesthesiologists for resuscitation and stabilization, and all had the capability to treat sepsis, do exchange transfusions, and manage intra-arterial lines. The level I hospitals were all those offering routine obstetric care that did not meet the criteria for level II or III designation.

Rural/Urban Classification

All 39 counties in Washington were categorized as to their relative urban or rural composition based on the percentage of inhabitants living in urbanized areas within the

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This research was supported by grants from the Fogarty Center, National Institutes of Health; the Medical Research Council of New Zealand; the W. K. Kellogg Foundation; and the Clinical Scholars Program of the Robert Wood Johnson Foundation.

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county. The counties were divided into four quartiles, with the 25% of counties that were most urbanized designated as urban and the 25% that were least urbanized designated as rural; the two intermediate categories were labeled semi-urban and semirural.

Data Sources and Analysis

Data from this study came from the Washington State linked birth and infant death records. Reporting of neonatal deaths is complete in Washington State, and all neonatal deaths are matched with the appropriate birth certificate.[12,13] Information abstracted from the record in each case includes the birth weight of the infant, the hospital of birth, and the age of the infant at the time of death.

After all public maternity hospitals in Washington State had been aggregated according to their level of care and their geographic location, the number of births and deaths was determined for each hospital level and geographic category. Each neonatal death was assigned to the hospital where the infant was born, regardless of the ultimate place of death. A death that occurred in a level III hospital after a neonatal transfer, for example, would be attributed to the hospital where the infant was born. The proportion of infants weighing less than 1,500 grams at birth, the crude death rate, the birth-weight-specific mortality rates, and the standardized neonatal mortality ratios were then calculated for each hospital in Washington State, for levels I, II, and III hospitals aggregated together into groups, and for hospitals in the four rural-urban categories. Increments of 250 grams were used as birth-weight categories, and the outcome for each hospital was indirectly standardized by birth weight to the combined mortality experience of all the hospitals in this study.[14]

Results

From 1980 to 1983, there were 264,618 live births and 1,571 neonatal deaths in the 90 Washington State hospitals that routinely provide obstetric care. The system is highly regionalized; although 45% of all births occurred in level I hospitals, only 16% of the very-low-birth-weight births (less than 1,500 grams) and 35% of the low-birth-weight births (1,500 to 2,500 grams) occurred in those hospitals. Table 1 compares the hospitals grouped according to their designated level of care. The case mix of the hospitals—as measured by the proportion of births of less than 1,500 grams—is related to the level of care. The proportion of infants of very low birth weight born in level III hospitals is almost eight times greater than that in level I hospitals. As expected, crude neonatal mortality rates are correlated with the proportion of infants of very low birth weight born in each group of hospitals.[15] These findings are consistent with a regionalized

TABLE 1.—*Neonatal Outcomes in Washington State by Hospital Level, 1980-1983*

Hospital Level	No. of Hospitals	Total Live Births	Births <1,500 grams, %	Crude Neonatal Mortality Rate (per 1,000 births)	Neonatal Deaths Observed	Neonatal Deaths Expected*	Standardized Neonatal Mortality Ratio	(95% Confidence Interval)
I	73	118,220	0.32	3.82	452	444	1.02	(0.93-1.12)
II	11	83,560	0.44	4.55	380	368	1.03	(0.93-1.14)
III	6	62,838	2.49	11.76	739	759	0.97	(0.90-1.05)
Total	90	264,618	0.87	5.94	1,571	1,571	1.00	

*Based on 1980-1983 Washington State births standardized by birth weight.

TABLE 2.—*Birth-Weight-Specific Births, Deaths, and Neonatal Mortality Rates in Washington State by Hospital Level, 1980-1983*

	Level I Hospitals, N=73			Level II Hospitals, N=11			Level III Hospitals, N=6		
Birth-Weight Group, grams	Births	Deaths	Rate	Births	Deaths	Rate	Births	Deaths	Rate
<1,500*	381	177	464.57	368	169	459.24	1,563	496	317.34
1,500-2,499	4,019	84	20.90	3,085	63	20.42	4,495	119	26.47
2,500-4,499	110,512	158	1.43	77,606	124	1.60	55,378	98	1.77
≥4,500†	3,308	33	9.98	2,501	24	9.60	1,402	26	18.54

*Mortality rate for level III hospitals is significantly lower than for level II hospitals ($P < .0001$, $\chi^2 = 26.56$; 2 degrees of freedom [*df*]) and level I hospitals ($P < .0001$; $\chi^2 = 29.34$; 2 *df*).

†The observed number of neonatal deaths differed significantly from that expected by chance across the three hospital levels ($P < .0225$; $\chi^2 = 7.59$, 2 *df*).

TABLE 3.—*Neonatal Outcomes in Washington State by Rural-Urban Location of Hospital, 1980-1983*

Rural-Urban Location	No. of Hospitals	Total Live Births	Births <1,500 grams, %	Crude Neonatal Mortality Rate (per 1,000 births)	Neonatal Deaths Observed	Neonatal Deaths Expected*	Standardized Neonatal Mortality Ratio	(95% Confidence Interval)
Rural	15	7,163	0.25	3.63	26	23	1.15	(0.75-1.68)
Semirural	19	19,637	0.32	4.02	79	75	1.06	(0.84-1.32)
Semiurban	26	80,710	0.47	4.63	374	345	1.08	(0.98-1.20)
Urban	30	157,108	1.18	6.95	1,092	1,128	0.97	(0.91-1.03)
Total	90	264,618	0.87	5.94	1,571	1,571	1.00	

*Based on 1980-1983 Washington State births standardized by birth weight.

TABLE 4.—*Birth-Weight-Specific Births, Deaths, and Neonatal Mortality Rates in Washington State by Rural-Urban Location, 1980-1983*

Birth-Weight Group, grams	Rural Hospitals, N=15			Semirural Hospitals, N=19			Semiurban Hospitals, N=26			Urban Hospitals, N=30		
	Births	Deaths	Rate	Births	Deaths	Rate	Births	Deaths	Rate	Births	Deaths	Rate
<1,500*	18	5	277.77	62	24	387.10	378	176	465.61	1,854	637	343.58
1,500-2,499	229	6	26.20	692	17	24.57	2,930	59	20.14	7,748	184	23.75
2,500-4,499	6,719	15	2.23	18,312	31	1.69	75,017	118	1.57	143,448	216	1.51
≥4,500	197	0	0.00	571	7	12.26	2,385	21	8.81	4,058	55	13.55

*Mortality rate for urban hospitals is significantly lower than for semiurban hospitals ($P < .0001$; $\chi^2 = 20.19$; 3 degrees of freedom).

system in which prenatal referral and intrapartum transfer of high-risk mothers are commonplace.

Standardized mortality ratios (SMRs) are computed by determining the number of deaths that would be expected if the outcome achieved by the hospital or hospitals in question were applied to the birth-weight distribution of all the babies in the state.[14] As can be seen from Table 1, the SMRs for each level of care are near unity: none of the observed differences are statistically significant.

Table 2 shows the birth-weight-specific neonatal mortality rates for these same hospitals aggregated by level. Although the standardized mortality ratios are similar across the levels, the pattern of birth-weight-specific neonatal mortality rates observed for level III hospitals is notably different from that prevailing in level I and level II facilities. Level III hospitals have significantly lower mortality rates for infants weighing less than 1,500 grams at birth but higher rates for infants weighing more than 4,500 grams. Level I and level II hospitals have outcomes that are similar for all birth-weight groups.

Table 3 analyzes hospital performance by the rural or urban location of the county where a hospital is situated. There is a definite gradient, from the 15 hospitals in the most rural counties to the 30 hospitals in the most urban counties. Rural hospitals—all of which are level I—have few low-birth-weight births and a commensurately low crude neonatal mortality rate. Urban hospitals are at the other end of the spectrum, with relatively more infants with a low birth weight and a higher crude neonatal mortality rate, reflecting the fact that all the level III centers are located in urban counties.

Analyzing the SMRs for rural-urban location shows that there are only small differences in standardized neonatal mortality. The SMR for the hospitals in the most rural counties is 1.15, in contrast to an SMR of 0.97 in the most urbanized counties. Neither of these differences is statistically significant, however, despite the appearance of a trend. It should be noted that while hospitals in the most rural counties do have a slightly higher standardized mortality, the number of excess deaths—the difference between the number observed and the number expected—is only three and the associated 95% confidence interval is wide, that is, 0.75 to 1.68.

Table 4 lists the birth-weight-specific neonatal mortality figures for hospitals classified according to their rural-urban location. No discernible pattern emerges. The rates for infants of very low birth weights differ substantially, but the lowest rates are at the two ends of the spectrum—the most rural and the most urban counties—with only the difference in rates between urban and semiurban hospitals reaching statistical significance. Only 3.7% of all low-birth-weight babies (less than 2,500 grams) were born in the 34 hospitals of the state's rural counties, while 10.1% of all babies are born in these hospitals, and the outcomes for these infants are similar to the much larger number of babies born in urban

TABLE 5.—*Comparative Neonatal Outcomes in Hospitals With Level II and Level III Obstetric Units, Washington State, 1980-1983*

Hospital Identifier	Hospital Level	Total Live Births	Births <1,500 grams, %	Crude Neonatal Mortality Rate (per 1,000 births)	Neonatal Deaths Observed	Neonatal Deaths Expected*	Standardized Neonatal Mortality Ratio (95% Confidence Interval)
1	III	8,339	7.79	27.22	227	276	0.82† (0.72-0.94)
2	III	10,351	1.55	7.92	82	85	0.96 (0.76-1.19)
3	III	11,109	1.72	8.91	99	99	1.00 (0.81-1.21)
4	III	9,465	1.02	5.81	55	55	1.00 (0.75-1.30)
5	III	11,005	1.72	10.00	110	102	1.07 (0.88-1.29)
6	III	12,569	2.20	13.21	166	140	1.18† (1.01-1.38)
7	II	8,078	0.28	2.97	24	31	0.77 (0.50-1.15)
8	II	2,740	0.51	3.65	10	11	0.88 (0.42-1.63)
9	II	9,023	0.34	3.21	29	34	0.86 (0.58-1.24)
10	II	5,990	0.30	3.34	20	22	0.89 (0.54-1.38)
11	II	9,159	0.48	4.15	38	41	0.93 (0.66-1.28)
12	II	13,630	0.32	4.26	58	55	1.05 (0.80-1.36)
13	II	6,843	1.23	8.18	56	53	1.06 (0.80-1.37)
14	II	8,669	0.35	4.50	39	35	1.12 (0.80-1.53)
15	II	5,919	0.52	5.07	30	25	1.22 (0.82-1.74)
16	II	7,161	0.42	5.87	42	34	1.22 (0.88-1.65)
17	II	6,348	0.30	5.36	34	27	1.28 (0.88-1.78)

*Based on 1980-1983 Washington State births standardized by birth weight.
†Difference between observed and expected deaths significant at the $P < .05$ level.

hospitals in the state. The data presented in Table 4 reinforce the conclusion that possible geographic differences in hospital outcomes have been largely mitigated by the regionalization of perinatal services.

Table 5 explores differences among individual level II and level III hospitals within the state. It is clear that hospital 1 occupies a unique position within the state, with almost 8% of all births occurring here being infants weighing less than 1,500 grams. The next highest proportion of very-low-birth-weight infants in an individual hospital is less than a third that percentage. Of all neonatal deaths occurring in the state, 14% are assigned by birth to this facility, which obviously has a tertiary referral role unlike that of the other level III centers. It is interesting to note that this hospital's SMR is the lowest of the level III hospitals and is the only outcome in any of the level II or level III hospitals that is significantly lower than the population experience.

By contrast, hospital 6 has an SMR that is significantly higher than that for the population as a whole. Although it has a high proportion of very-low-birth-weight infants, the outcomes in this institution are not as good as those achieved in the other level III facilities in the state. The number of excess deaths in this hospital is 26, more than the number of excess deaths that occurred in all the level I and level II hospitals in the state.

The state's level II hospitals are relatively homogeneous, with one exception. Hospital 13 resembles a level III hospital with a relatively large proportion of infants with very low birth weights, nearly three times that of the average level II hospital. None of the SMRs for the level II hospitals are significantly different for the experience of the state's hospitals as a whole. As noted earlier, level II hospitals are similar to level I hospitals, the major difference noted in this study between the two groups being the larger number of deliveries in level II hospitals.

Discussion

The objective of regionalizing perinatal care is to improve outcome by matching the clinical requirements of the mother and infant with the technologic capacity of the hospital and professional staff. Because only a relatively small proportion of infants requires neonatal intensive care—usually for problems associated with a low birth weight—and because perinatal outcome improves with clinical experience and volume, regionalization provides a way to concentrate these cases in a small number of institutions that have the expertise needed to care for these children.[2]

The regionalization of perinatal care has two central features: categorizing individual hospitals according to their technical and professional capacity to deal with cases of varying complexity, and linking individual hospitals and physicians within specific geographic areas into regional systems that facilitate the referral and transfer of mothers and babies to locations with the appropriate level of care.

In the ideal regionalized system, high-risk babies would be born predominantly in level II and level III hospitals, while level I hospitals would concentrate on the care of low-risk mothers and babies. To accomplish this result, high-risk mothers living in areas served by level I hospitals—particularly those living in rural areas—would be identified and transferred to higher level facilities before delivery, thus benefiting from the technical capacity at the more technically sophisticated hospital.

The Extent of Perinatal Regionalization in Washington State

The location of the births of very-low-birth-weight infants provides a direct measure of the extent of perinatal regionalization. In the ideal system there would be no births of infants weighing less than 1,500 grams in level I hospitals, particularly those in rural areas. By this criterion, Washington State has made substantial progress in creating a successful regionalized perinatal care system. Only 16% of these infants are born in level I facilities, and only 3.5% are born in rural hospitals, although these facilities are responsible for 45% and 10.1% of all births in the state, respectively.

These data indicate that referral or transfer of high-risk mothers is the rule rather than the exception. Most of the transfers appear to flow directly to level III facilities. Of all infants with very low birth weights, 68% are born in the state's level III hospitals, although only 24% of all births occur in these facilities. The birth-weight distribution of infants born in level II hospitals is much more similar to that in level I than it is to that in level III facilities. These data suggest that level II hospitals play only a limited role as the destination of maternal transfers from level I institutions.

Level of Care and Neonatal Outcome

The best available measure of the quality of perinatal care is birth-weight-specific neonatal mortality. In this study, the overall differences between level I, II, and III hospitals—as measured by the standardized mortality ratio—were negligible. Level III hospitals, however, had significantly lower mortality rates for infants weighing less than 1,500 grams and higher rates for infants weighing more than 4,500 grams than those recorded in level I and level II hospitals.

The lower mortality rates in level III hospitals for very-low-birth-weight infants is to be expected. The basic premise of regionalizing perinatal care is that prompt access to an experienced neonatal intensive care unit is associated with higher survival rates, and the data here confirm the findings of other authors.[5,6,16-19] In addition, Horwood and coworkers have shown that selection biases associated with prenatal transfer tend to lead to better apparent outcomes in referral centers, an effect that probably plays a role in explaining the findings noted here.[20] Only population-based studies—rather than center-based studies—can determine the relative importance of these two findings in Washington State.

The higher mortality rates for large infants in level III facilities have been noted previously in other studies and have several possible explanations.[21-23] Maternal referrals and transfers of high-risk patients with relatively large infants to level III centers could lead to higher neonatal mortality rates in these birth-weight groups. Conversely, it is possible that normal- and large-birth-weight children have better outcomes in less technologically intense settings by avoiding potential iatrogenic complications. Comparing birth-weight-specific outcomes for those children who are referred to level III centers with those who receive their prenatal and intrapartum care at level I or level II centers would help to clarify this issue.

Rural Obstetrics and Neonatal Outcome

There are 34 level I hospitals in the predominantly rural counties in Washington State, accounting for 10% of all the

births in the state. The evidence suggests that these hospitals are assiduous in referring high-risk mothers for delivery in more sophisticated facilities: only 80 infants with very low birth weights were born in these hospitals during the four-year study period, and their neonatal mortality rate was similar to that achieved in urban hospitals. It can be argued, however, that any high-risk infant born in these facilities represents a failure of regionalization and that these hospitals, by their very presence, constitute a hazard because not every high-risk mother can be identified and transferred before delivery.

The standardized mortality ratios are reassuring in that rural hospital outcomes, taken as a whole, do not deviate significantly from the population norm.[16,24] Even with meticulous prenatal screening, not all cases of premature labor can be detected in time to arrange for maternal transfer. In addition, rural hospitals are a valuable resource in the management of unanticipated obstetric emergencies. Given that rural hospitals play an important role in stabilizing health care systems in small communities and that exporting all pregnant women to other communities for their obstetric care exacts substantial financial and emotional costs, rural hospitals have an important and legitimate role to play in obstetric care.

Future Improvements in Neonatal Outcome

The results of this study suggest that Washington State has been successful in implementing a regionalized perinatal care system and that significant geographic differences in neonatal outcome have been virtually eliminated. It appears that most infants have the benefit of neonatal intensive care when indicated and that most transfers of very-low-birth-weight infants occur before birth. Neonatal mortality rates in level 1 hospitals and in rural hospitals are similar to those in larger, more technologically sophisticated facilities.

The most promising strategy for further reducing the neonatal mortality rate is to decrease the proportion of very-low-birth-weight births. The 0.87% of babies who weigh less than 1,500 grams at birth account for 53.6% of all neonatal deaths in the state. Programs that are effective in preventing preterm births will have an immediate impact on the neonatal mortality rate.

The Future of Regionalized Perinatal Care in an Era of Competition

Regionalized perinatal care systems depend on cooperation among hospitals and physicians. Each unit is part of a larger system that defines the roles and relationships existing among professionals and institutions. As competition among hospitals becomes more intense and well-trained perinatologists and neonatologists diffuse out from the training centers into community hospitals, community hospitals will tend to retain more high-risk patients. If carried to an extreme, this may frustrate the intent of regionalization: to concentrate large volumes of high-risk patients in a limited number of centers that can develop the expertise and the experience needed to deal with the clinical demands of this group of patients.

There is excellent evidence that outcomes are better, particularly for technically complex clinical undertakings such as neonatal intensive care, in centers with a high volume of patients with special needs.[25] This study adds support to that conclusion: 28% of all the babies weighing less than 1,500 grams were born in one facility, yet the associated neonatal mortality rates for this group of infants were much lower than for other hospitals in the state. To the extent to which the proliferation of neonatal intensive care units in other hospitals limits the number of referrals, or changes referral patterns, neonatal outcomes may deteriorate.

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Medical Education

Medical Education—Three-Legged Stool or Five-Wheeled Work Chair?

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I am going to speak about medical education, reflecting first on the substantive change in what we call "patient material" on the inpatient units, the changes in clinicians' experience with these patients, and the resulting impact on the education of students and house officers. Considering both exposure to the facts of clinical medicine and the acquisition of capability in its practice, I will then examine the nature of the process by which young physicians develop expertise. Finally, I will move beyond that tripod of goals—knowledge, skills, and attitudes—that seems to drive the curriculum of the medical school and conclude by exploring additional considerations that are important enough to turn the triad (the three-legged stool) into a pentad (the five-wheeled work chair).

With the recession of the 1980s, American business began examining its operating bottom line in detail and not only discovered the relatively large chunk of its pretax profits that went toward health care premiums for workers but also uncovered the revelation that a market that had dictated to them for years was, in fact, theirs. When the Washington Business Group on Health first assembled, gathering several dozen of the nation's largest employers, nothing may have been more astounding to them or more important to us than the appreciation of the fact that only a handful of American employers purchased health care for some 25% of the population of this nation. And when one is that good a customer, they recognized, one moves into a buyer's market. The power had shifted in the physician-patient-hospital-payer dynamic, and, as a result, a series of controls has emerged, all too familiar by now. The impact has been of major consequence to both office and hospital procedures, to patient convenience, comfort, and care, and to the educational opportunity provided our trainees.

Let's examine the changes taking place in inpatient care. Earlier discharge, admission on the morning of an operation, and more stringent requirements on justifying admission all make for an increased intensity of illness on the average, which means not only an increased use of resources but also an increased pace of work for residents, increased stress on the job, a greater demand for work performance and productivity, and less time available for reflection and personal study. The psychological space of the inpatient unit has shifted, too. With sicker patients or, rather, with more patients in the sicker phases of their illnesses, and with earlier discharges, the opportunities for gratification—seeing clearly that one has done well for a patient—are less available to counterbalance the mounting stress.[1] Furthermore, to the extent that an inpatient admission is related primarily to the carrying out of a complicated diagnostic or therapeutic procedure, the learning experience tends to shift toward technology disembodied from the person and isolated from the exquisite responsibility and privilege of the physician-patient relationship.

Even more significant than these shifts in intensity, stress, and psychological reward is the qualitative change in what we once labeled "patient material"—that is, in the specific nature of the illness with which a house officer contends. Today there is a trimming of the spectrum of illness welcomed by third-party payers on the inpatient unit. Yet education in clinical medicine calls not simply for a disembodied awareness of the pathophysiology of a disease during its most intensive phase, but rather an experiential familiarity with as full a spectrum of the illness as is practicable, ideally from cause to cure or defeat. To the extent that we truncate the trainees' involvement in that full spectrum by shaving days off both ends of the inpatient experience, we are altering the subject matter of that education. We are altering the quality of that education.

It is a matter of more than lost days and more than vanished experience with an appropriately broad spectrum of illness. Preoperative physical examinations and tests done in anticipation of admission typically are now done by others, rather than the house staff later assigned to the actual inpatient admission. Medical patients bring pressures for the admitting internist—in advance of a patient's arrival and of a student's and resident's workup—to schedule essential diagnostic procedures and critical consultations. Such alterations in the nature of the process of inpatient care create a major qualitative disruption to the trainees' cognitive experience, clearly altering the education to be derived.

In many teaching hospitals, there is a sharp change of pace. Where census has not declined parallel to the drop in length of stay, as at Boston's Beth Israel Hospital, there are more admissions. To the business office this growth in market share may be a happy event, but it represents a tightening of the noose on the department chairs as well as the house staff because, in most cases, there has not been a comparable increase in house-staff numbers to compensate. Payment limits prevent the recruitment of more residents or other professional help.

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For example, at Beth Israel Hospital, medical and surgical beds remain occupied at 90% despite a significant decline in length of stay. Each year we seem to admit more patients who stay for fewer days. In the past we have increased house-staff numbers somewhat but can afford additions no longer. As a result, we have had to rearrange residents' schedules in medicine, taking them from other rotations to create a night-time relief corps so that no resident regularly assigned to an inpatient unit will have to work up more than six patients on a given day.

When I was a house officer at the Massachusetts General Hospital in the Department of Medicine, two or three admissions was a reasonable expectation. Four was a heavy load, five was heroic, and six—which might have come about once a month—won you a place in the hall of heroes in house-staff mythology and a well-phrased compliment from Holly Smith, who was then chief resident. Today, how well can one work up six sick patients in one evening? How well can one keep them clear in one's mind? How well can one manage those cases? And, is this the way to learn medicine?

Look at the surgical house officer. At Beth Israel, about 40% of patients having inpatient surgery are same-day admissions. The resident's experience, therefore, is often a hurried and harried preoperative check; the real contact becomes that with an operative field and not with a person. How does that truncated experience relate to the awareness a surgical resident will require when he or she is in practice? To the extent that most trainees will spend most of their careers dealing with much of those things we have now moved out of the inpatient experience, how valid does today's teaching hospital inpatient experience remain as the basic core of medical training?

In the past, the set of activities that involve the management of patients pretty much overlapped the set of activities that led to the desired education of our trainees. And the pace of work was such that time could be taken in the day's schedule of hospital work for discussion and reflection with peers and senior physicians. Today, however, those two sets of activities—the provision of care and management of patients, on the one hand, and the educational experience necessary for learning and mastering clinical medicine on the other—are increasingly divergent. That loss of congruence reflects our conclusion: the traditional teaching hospital inpatient experience, reshaped by contemporary financial pressures, is moving away from its time-honored role as the fundamental locus of curriculum for graduate medical training.

Let's now move beyond the *substance* from which trainees learn, for we teach more than facts to our students and house officers. Because medicine is both an art and a science, we are engaged as well in teaching them how to be physicians. David Eddy, a physician and mathematician, Director of the Center for Health Policy, Research and Education of Duke University (Durham, NC), comments on the complexity of medical decision making.[2] "One of the greatest accomplishments of the medical profession," he states, "is the development of methods that reduce the decisions faced by physicians to a manageable size and enable physicians to derive the correct answers." Focusing on three processes, making a diagnosis, selecting diagnostic tests, and choosing a treatment, he points out that the ninth revision of the *International Classification of Diseases* lists no fewer than 25,000 first-order codable conditions. There are about 3,000 biomedical journals, and MEDLINE, which contains the citations published in *Index Medicus,* has about 4.2 million records of scientific articles and each month adds about 25,000 more. Memory alone cannot be relied on even though most physicians do, in fact, acquire, store, and are capable of retrieving in a reasonably orderly fashion vast amounts of information.

Even having the facts is meaningless in the face of inadequate information processing for diagnosis. Eddy observes

> [H]umans are notoriously poor at manipulating probabilities . . . [but they] are excellent at making one-by-one comparisons. The diagnostic heuristic transforms the diagnostic problem from a calculation of hundreds of probabilities into a smaller number of comparisons.

What is it that enables a capable clinician confronting a complex diagnostic problem to pick a few features of a patient's illness, use these to generate a list of possible diseases, consider these few possibilities one by one in relation to the explanation of most or all of the patient's signs and symptoms? It is at least in part a matter of matching patterns. But the question is, how are these patterns visualized and articulated? Eddy emphasizes, "the solutions developed by the profession to solve the diagnostic and treatment problems in the past do not work as well for the problems the profession will face in the future." It is not only the growth of knowledge, the burgeoning technology for diagnosis and treatment, and the limited experience that trainees confront in the inpatient situation. The rising costs of medical care, the controls superimposed by payers, issues of liability, increasing empowerment on the part of patients, and a greater sensitivity of clinicians to the needs of patients render the mastery of doctoring an ever-growing challenge.

How does this mastery develop? How does a trainee progress from novice to expert? The phrase, "from novice to expert,"[3] may be familiar to you. It is the title of a splendid volume by a colleague of yours, Patricia Benner, PhD, who is a nurse and a professor at the University of California, San Francisco, School of Nursing. Dr Benner's inquiry, as the subtitle of her book points out, is toward "excellence and power in clinical nursing." It deals with two subjects, both of which are worth study. One is a lucid exposition of what nursing really is, what nurses really do. The other, of relevance to our inquiry, examines the process in nursing practice of moving from novice to expert.

Some of Dr Benner's thinking derives from the studies of a mathematician and systems analyst, Stuart Dreyfus, and a philosopher, Hubert Dreyfus, who developed a model of skill acquisition out of their studies of chess players and of airline pilots. Their model delineates five levels of proficiency: novice, advanced beginner, competent, proficient, and expert. The movement from one to another level reflects changes in three general aspects of skilled performance: first, moving from relying on abstract principles to the use of past concrete experience as paradigms; second, a change in the learner's perception of the situation demanding a response—that is, where the situation is seen less and less as a compilation of equally relevant bits and more and more as a complete whole in which certain parts are more relevant than others; and third, the passage from detached observer to involved performer, no longer standing outside a situation but engaged in it. Benner interviewed pairs of nurses from several hospitals, each consisting of one beginner and one expert. The interviews focused on patient care situations the pair had in common. The nurses were asked to reflect on

clinical knowledge related to the situation that they had found particularly difficult to teach or to learn, and the reports were analyzed to see if there were characteristic differences in the two descriptions of the same clinical incident that might lead to some taxonomy in understanding the progress from novice to expert. Many interviews were held with other nurses as well.

Benner suggests that stage one, the novice, enlists persons with no experience of the situations in which they are expected to perform. Novices are taught about the situations they will confront in terms of objective attributes—weight, intake and output, vital signs, and the like—as Benner puts it, "features of the task world that can be recognized without situational experience." And they are taught context-free rules to guide action: for example, weight gain and an intake that is consistently higher than output by more than 500 ml could indicate water retention that would call for restricting fluid until the cause of the imbalance and further action are decided. Rule-governed behavior typical of the novice is limited and inflexible. Because there is no experience, rules must be given, but rules legislate against expert performance because they do not delineate the most relevant tasks.

Advanced beginners have coped with enough real situations to begin an awareness of "meaningful situational components" that are recognizable only in the light of past experience. For a nurse it might be, for example, a patient's readiness to learn about his or her ileostomy. Guidelines may be given by the instructor: Does the patient ask questions about the operation or the dressing change? Does the patient look at or handle the wound? Because these guidelines relate to the clinical situation and are not context-free rules, only an advanced beginner can begin to formulate actions as a result.

Stage three is competence, typified by the nurses who have been working in a similar situation for several years and now can see their actions in the light of longer term plans. Emerging from a perspective of experience, each plan is based on a conscious and analytic contemplation of the patient and the patient's problem, and it gives a competent nurse the beginning of a feeling of mastery, a sense of being able to cope with the many contingencies of clinical nursing. Competence brings about the conscious, deliberate planning that helps achieve efficiency and organization in a clinical endeavor. Benner points out, however, "There is a sophomoric quality to the competence stage. The clinical world seems organized, finally, after great effort."

Proficiency is the title of the fourth stage, and proficient performers begin to look at a situation as a whole, where the perspective is not so consciously thought out but rather "presents itself" based on experience and recent events. Proficient nurses understand immediate events in terms of the expected whole picture and are able to modify their plans in response to the uniqueness of a clinical course. Proficient nurses recognize when the expected normal picture does not materialize; they consider fewer options than do competent nurses and focus more sharply on the most meaningful region of a problem. Benner comments,

> The proficient performer is best taught inductively, by beginning with a clinical situation and having the performer supply his or her ways of understanding the situation. When situations are introduced that exhaust the performer's way of understanding and approaching the situation, then a fruitful area of necessary learning has been uncovered.

The uppermost stage, that of expert, may seem at first contrary to the traditional expectation. The expert does not rely on analytic principles—rules and maxims—to connect an understanding of the situation to an appropriate action. An expert nurse, Benner says, "with an enormous background of experience, now has an intuitive grasp of each situation and zeros in on the accurate region of the problem without wasteful consideration of a large range of unfruitful, alternative diagnoses and solutions." Experts operate from a deep understanding of the total situation and may well reply, when asked why they did something, "because it felt right," before going on to articulate in more comprehensible terms the reasoning of the earlier stages. Stuart and Hubert Dreyfus are quoted by Benner,

> As long as the beginner pilot, language learner, chess player, or driver is following rules, his performance is halting, rigid, and mediocre. But with the mastery of the activity comes the transformation of the skill which is like the transition that occurs when a blind person learns to use a cane. The beginner feels pressure in the palm of the hand which can be used to detect the presence of distant objects such as curbs. But with mastery the blind person no longer feels pressure in the palm of the hand, but simply feels the curb. The cane has become an extension of the body. . . . the performer is no longer aware of features and rules, and his/her performance becomes fluid and flexible and highly proficient. The chess player develops a feel for the game; the language learner becomes fluent; the pilot stops feeling that he/she is flying the plane and simply feels that he/she is flying.

In my mind, these are ideas of extraordinary insight, and they apply not only to nursing but have relevance to teaching and learning in clinical medicine. Certainly, the notion of moving from a context-free set of rules to a more holistic grasp of the complex clinical situation where one's diagnostic insights, further inquiry, and choices of therapy "feel right" even as they are articulated as defensible on the basis of specific knowledge, characterizes my senses of clinical competence. To me, the beautifully delineated decision trees, with their sets of multiple probabilities, represent little of the way that real medicine is practiced.

Looking at clinical medicine, Dr J. S. McCormick of the University of Dublin writes in *The Lancet* "that recognition, based on knowledge and experience, is the mainspring of diagnosis and that the diagnostic process is simple, straightforward and in need of demystification."[4] He argues that physicians presented with a symptom, the complaint that often opens a new consultation, immediately develop notions of its cause. The guesses develop from the age and sex of the patient, from the context of the illness, and from the specialty of the physician. In practice, he points out, symptoms are often simple: a sore throat speedily and properly leads the physician to having a look, typically without undertaking a systems review or inquiring about the patient's sexual history. The normal diagnostic tasks of physicians, he argues, are straightforward and do not rely on the imaginative generation of hypotheses but on knowledge and experience—knowledge of probability and the ability to recognize common presentations and physical abnormalities. The apparent diagnostic acumen of senior clinicians, he argues, may be in large measure déjà vu; having seen it before, they can now recognize it again. And experience may tend to protect against diagnostic error by enabling physicians to recognize those pieces of information that are discordant and ring warning bells to say that things may not be as simple as they seem at first. McCormick concludes,

> Diagnosis . . . is . . . the essential task of the physician. . . . it follows that an important part of medical education is learning how to make correct diagnoses and how to diminish the possibilities of error. . . . although knowledge and experience can lead to making the same mistakes with increasing confidence, they remain the basis of our diagnostic skill.

Also writing in *The Lancet* some four months later, Dr. E. J. M. Campbell of McMaster University (Ontario, Canada) emphasizes that problem solving is normally hypothetico-deductive, which is, he adds, "a fancy way of saying that, when faced with a problem, the usual approach is to think of possible solutions and test them."[5] He emphasizes, however, that diagnostic ideas of more or less specificity come to mind almost immediately in the physician-patient encounter, and experienced clinicians navigate their way through the histories, physicial examinations, and laboratory tests rather individualistically in solving problems rather than remaining tethered to a branching tree of diagnostic algorithms. They are not blank minds ritualistically collecting information, context-free, but rather more the holistic expertise emphasized by Benner. Algorithms do not represent the diagnosing mind.

Such considerations have major implications for education—as important as those that deal with what may be available as "patient material" to illustrate and teach the substance of medicine. Students should be faced with diagnostic problems soon after they begin the study of medicine, argues Campbell. Teachers should try to share with students the formulation of a hypothesis, the development of a map of the terrain under scrutiny, and the choice of routes. At each turn in the history, examination, and investigation, it is important to ask what are the implications of the findings to eliminate the pursuit of information that gets one no further and to focus on approaches that are problem solving rather than simply performing routines.

The editor of *The Lancet,* reflecting on these views, asks why the process of diagnosis is seldom found in conventional medical school curricula, even though it is the principal intellectual skill of medicine.[6] Medical schools continue to emphasize the rote learning of a myriad of facts felt to be fundamental to the subsequent diagnostic process, but they do not teach how to manipulate such information. Medical students must be taught to practice medical thinking, to understand what they are doing with the information they have and to learn to use that evidence to reject unacceptable diagnoses. We may argue whether diagnostic recognition per se is or is not hypothesis generation, and we may tilt toward the cognitive psychologist's position that diagnosis is primarily a "hypothetico-deductive" process or side with Benner in a more holistic view that only seems less sophisticated because we do not fully understand the process of moving from novice to expert. The important point is that as teachers of medical students and house officers, we must go beyond the considerations of what has changed in the "patient material" available to trainees and think equally hard about the processes by which clinicians use the information they acquire and how best to teach these as well. Our responsibilities as mentors thus broaden as our own perspectives enlarge on teaching and learning in medicine.

To summarize our discussion thus far, we have considered the changing content of illness displayed to trainees on inpatient units. We have considered the resulting change in the tasks that are the responsibilities of the trainees. From the truncation of the spectrum of illness seen and from the move of many of the cognitive and physical tasks of inpatient care to the ambulatory sector immediately before and after admission to hospital, it appears that the inpatient rotations have become far less able to provide the substance, the experience, and the perspective needed to gain mastery in clinical medicine. Because the eliminated segments—what yesterday helped make whole the inpatient experience—because these portions of illness have been moved into the ambulatory sphere, it is only natural that educators look to the clinic and the office as substitutes for what has been lost on the wards and floors. But it is not a one-to-one tradeoff, and our examination of the nature of expertise explains why. If the development of expertise is characterized by the shift from context-free rules with little differentiation of what is important from what is not to a garnering of experience that not only makes for such differentiation but integrates individual vignettes and scenarios of illness that allow clinicians ultimately to feel what is right and to articulate it in more formal, even algorithmic, terms, then educators must consider that the new ambulatory experiences must be integrated with the inpatient exposure in a way that is most meaningful to the educational process. We cannot create a proper sense of the organism by tacking the head of a duck onto the body of a horse and the tail of an armadillo.

We have moved, thus far, from the content of medicine to a consideration of its diagnostic process—the use of that content. The traditional framework for such considerations in medical education has been the examination of what *knowledge, skills,* and *attitudes* we want to engender in medical school graduates and in young physicians completing residency programs. Well and good. But while this triad is an important component of the objectives of medical education, it is not sufficient. Two additional imperatives enter the considerations of educating physicians: expanding this triad to a pentad. They are the gratification of being physicians and the reassurance of relative personal immunity in physicians' struggle with death and disease.

In the "old days," at the height of the Oslerian tradition, the inpatient unit served as an ideal arena for teaching and learning because, as we have pointed out, many of the inpatients then provided most of the entirety of an acute illness—a history with symptoms, physical findings on examination, the opportunity to go through a diagnostic process, develop therapeutic decisions, and to see firsthand the direction of outcome. But also the essence of a physician's role and knowledge and power could be exemplified in such admissions. Not only were they each a practicum of a chapter or two in a textbook of medicine, but working on each case foretold what it would be like to practice medicine fully fledged.

We all recognize that virtually every physician takes away from medical school and house-staff training vivid imprints of physician-mentors whose major lessons have been not merely the substance of medicine but also—and perhaps even primarily—the art and science of its practice, that is, lessons in intellectual integrity, empathy, sensitivity, and selflessness. While learning the material of medicine, physicians could see their persona and career being forged out of the direct examples of professors.

There was something, for example, in the classic ward routines of house-staff training. The arrival of the visiting physician, a person of stature, was a highlight of the day. The circuit made around the unit, even by the most self-effacing of these mentors, followed by a diligent troop ranging from medical students to senior residents, provided a certain measure of theater. By "theater" I mean not the histrionics of the more flamboyant of our colleagues but, rather, the drama inherent in the masterful performance of the expert physician

role and the resulting impression it makes. Consider two uses of such ritual that we cannot ignore, as we contemplate today's metamorphosis of the inpatient unit, the major clinical training site for the transition of student into physician. The first has to do with the gratification of being a physician. New responsibilities are being shouldered by students and even greater burdens, along with increasing accountability, by house officers. A growing and new effort is being demanded of them, and encouragement is important. With the classic rituals of the inpatient unit, of which the major rite, visit or attending rounds, is reinforced day after day, the high status of "doctoring" is affirmed daily. Through repeated affirming, the trying entry of the neophyte into the profession of medicine is nurtured repeatedly through the palpable promise of a future sense of professional self-confidence and even admiration from others. The trainee becomes inspired; he or she is doing something good, albeit difficult.

In the absence of apprentice relationships of students with senior physicians able and willing to teach, little of this sustenance appears at present in the ambulatory sector, to which we look more and more as a site for training. There the individual scheduling of patients and physicians necessarily eliminates most opportunity for such group reinforcement; as presently taught, there is little comparable "theater" in ambulatory care. The potential gratifications more often tend toward the purely cerebral, and the joys of outpatient practice pale in comparison with the hush that fell over an inpatient unit as the professor arrived for daily rounds and the gratification of taking part, once again, in a time-honored ritual.

A second aspect of our inpatient rites may be even more important. Not only are physicians given extraordinary responsibility along with extraordinary opportunity, as students they also begin an initiation into forbidden realms. Physicians become entitled to probe private parts of body and mind; they learn to hold a person's heart in their hands, stop it, and then set it going again—or not! Advancing into the realm of the forbidden, physicians take on death and dying as adversaries—a fearsome business. Recall that the role of healer—medicine man or woman, shaman, physician—existed long before those healers were actually able to do much about the maladies they were called to heal, beyond the promises implied to patients and family. But always there was a certain dramatic ritual that served not only to convince a patient of the shaman's power but perhaps also to reassure practitioners of their relative immunity from the horrors of the forbidden world with which they wrestled.

I suggest that this imputing of powers is needed by both patients and practitioners. If so, then it is not enough to argue that as the substantive basis—the so-called patient material that best presents the content of medicine for learning—moves from the inpatient unit to the ambulatory sector, so will trainees' psyches as readily make the same transition. It is not enough to conceptualize the knowledge, skills, and attitudes we want to develop in trainees. Academic medicine has taken several decades of learning to think of patients as whole persons, not simply clusters of symptoms and signs. We must also think of trainees as wholes, and that includes asking how we can support them as persons as they move into those disturbing realms of death and disorder, as they require and deserve the nurture, gratification, reassurance, and protection justly accorded healers. Intentionally or not, teaching hospitals shaped past inpatient unit routines to provide these necessities. Now, because the character of inpatient care and its role in teaching are changing so profoundly, our challenge expands to create comparable and realistic models for success in the teaching arena of ambulatory care, models that recognize not only the substantive requirements and their mastery, but also the psychological requirements for the "complete" physician.

In summary, we have examined the changing content of clinical material available to trainees and considered the impact of that change on medical education. We have gone further to probe the nature of the acquisition of that expertise we hope to inculcate. Finally, we have concluded that goals focused on knowledge, skills, and attitudes are not enough. That triad should be expanded to a pentad. As educators we must include both *gratification* as reward for assuming the responsibilities of the physician, and *reassurance*—the forging of a sense of relative immunity against God's wrath for probing the unconscious taboo of death, for jousting with it, and even, sometimes, for winning. How we contend with the burgeoning factual content of medicine, how we grow to understand the process of acquiring expertise, and how we create this theater of the psyche while hewing to the reality of today's science, economics, and ethics will be a major challenge to medical education for the 21st century.

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Medicine in Perspective

The Yin and Yang of Medical Practice

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EDITOR'S NOTE: *This article is adapted from papers presented at a meeting of the Hawaii Chapter of the American College of Physicians entitled "The Profession in Turbulent Times," held in November 1986, to reflect on some of the phenomena that are so greatly changing our profession. It contains considerable food for thought and a note of hope.*

The concept of yin and yang, as postulated in the Tao Te Ching, is difficult for persons raised in the Judeo-Christian ethic to grasp. The yin and yang do not refer to moral concepts such as good or evil, one emanating from God and the other from the devil. Rather, they are two contrasting and coexisting opposites. They are present in all things, inseparable, and function together in constant interaction, each preponderating and moderating in its turn. Rather than the eventual triumph of yang over yin, balance and harmony between these contrasting forces is the ultimate goal.

And so it is with medicine, we would propose. It has its yang, the components of which are hopeful and positive, and its yin, pessimistic and negative. To the yang belong the physician-patient relationship, the relief of pain and suffering, and the avoidance of an untimely death. To the yin belong the business, politics, and perhaps even the technology of medicine. There is a need for each; the impulse to take sides in this intricate interaction, warring against one or the other, should be resisted.

The Yang of Medicine

We will learn more about combating disease and keeping people healthy in the next 10 years than we have in the past 100. As practitioners of medicine, we will have the enormous satisfaction of using this new knowledge in the care of our patients.

The accelerated acquisition of new knowledge regarding the fundamental nature of disease and new remedies will continue, as will new and improved technologies. The replacement of old or damaged organs and the ability to outwit microorganisms will continue to improve. If the acquired immunodeficiency syndrome had appeared 20 years ago, we would have been terrified as to the future of all of us. Today, most of us feel confident that we will have an effective treatment within the next decade. Our often criticized technology will expand, and costs will decrease. This expansion of knowledge will make our job easier but not necessarily more enjoyable, because it is our relationship with our patients from which pleasure ensues rather than from the curing of disease.

The practice of medicine is a complex process that includes all of the professional activities that have to do with the science and art of diagnosing, treating, curing, and preventing disease, relieving pain, and preserving health. The care of a patient is a much different process from that of treating a disease—one very individualistic and personal, the other general and impersonal. Patient care requires something more than skill and knowledge. It is this intangible, poorly defined quality that transforms a good result into an almost mystical experience. Just what that quality is no one knows, but most physicians have felt it. What seems clear is that it is rooted in the humanistic philosophy that forms the basis of western thought. The underpinning of this philosophy is the dignity of the person.

Family physicians at the turn of the century were institutions unto themselves; their profession was a sacred calling with a duty to serve all regardless of race, creed, or financial status. They knew their patients and their financial status. They were rather haphazard about sending out their bills. Collection agencies did not include physicians as their customers.

The physicians resisted the changes taking place all around them. Their altruism and idealism seemed out of place in a society increasingly dominated by business. The medical profession was tagged as a cottage industry in an industrialized world. It was considered unethical to advertise abilities in any form.

But by the early 1930s even outsiders were noting changes in the practice of medicine. In 1932, Walton Hamilton, Professor of Law at Yale, wrote,

> The pressures from the system within which they must live and work are slowly and insidiously, but rather surely bringing to the physician a consciousness of his own pecuniary interests, making something more of a businessman out of him, and converting the thing once called "private practice" into a system of individual business competition. Its very character is out of harmony with the spirit of the profession.

Francis W. Peabody, MD, in a talk to the Harvard medical students in 1927, said, "According to older practitioners, young graduates have been taught a great deal about the mechanism of disease but very little about the practice of medicine—more bluntly, they are too 'scientific' and do not know how to take care of patients." We still hear similar statements; all of us know, however, that the young graduates of today are far better equipped to take care of patients than we were when we were young. Those of tomorrow will be even more capable than all of us. The seeds of change have been sown.

(Botticelli MG, Gilbert FI: The yin and yang of medical practice. West J Med 1988 Jul; 149:108-110)

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The Yin of Medicine

Many physicians disdain the federal government and labor unions as much as any other groups in our society. It is, therefore, the ultimate irony that these groups have done so much to create the opulent health care structure from which we receive so much. The demand of unions for adequate care for their members and the federal government's decision to underwrite health insurance for the elderly and poor have resulted in phenomenal growth in the health industry. Business and organizational expertise has been drawn into the administrative vacuum that resulted. This was inevitable, for the existing structure, consisting of loosely managed hospitals and unorganized practitioners, could not hope to cope with this growth.

It was also inevitable that the corporate model, with all its imperfections, be chosen as the basis for this reorganization. Its hierarchical decision-making apparatus, marketing expertise, and ability to capitalize large investments are but a few of its advantages. It is, however, in clear contradistinction to the traditional organization of the practice of medicine, where individual practitioners' close relationship with patients is the goal; the organization—hospital, third-party carriers, the federal government—is there only to support.

Physicians are ambivalent about this change. The administrative benefit is clear. On the other hand, the independent physician as an entity in the corporate model is an anachronism. This unstable relationship generates painful adjustment. Physicians have increasingly become employees of corporations instead of remaining private entrepreneurs. Even those who have chosen the traditional model are finding their lives and practices violated by progressively more irritating intrusions.

The American automobile industry provides an example of the deficiencies of the corporate model. The tendency to sacrifice quality for the bottom line and the use of marketing as a substitute for producing a good product are good examples. As decisions are made on an organizational basis, responsibility for those decisions is diffused, with a deleterious effect on quality. Leadership in these organizations increasingly passes from the hands of physicians (because of inadequate training) to managers (who lack firsthand experience with patient care). The sense of excellence that comes only with having had patient care experience inevitably suffers.

Likewise, some physicians are seduced by profits. They have joined the corporate forces in our industry to prey on patients' fears of death and ill health to sell their services. They have resisted defining quality when it appeared it might affect their incomes. To make themselves more competitive, they use technologic advances indiscriminately, even before their value is proved.

Yet, the potential from technology is enormous. Extraordinary diagnostic capabilities now exist; diseases once considered incurable are now easily treated, and some, such as polio and smallpox, have been virtually eradicated. The price: dehumanization. Intensive care beds are often occupied by people kept alive needlessly. Some cancer patients are brutalized with medications that carry little hope of changing the course of their illness. Some physicians' practices have been depersonalized to a point where patients are rarely touched and talked with but often x-rayed and otherwise invaded. Nothing has damaged the image of the physician more than this misuse of technology.

The evidence that the stature of physicians in our society has diminished is incontrovertible. The results of public opinion polls, the increasing number of malpractice suits, and the emergence of vociferous proponents of patients' rights all attest to this. Furthermore, hospitals and third-party carriers see physicians as impediments to their missions, and the federal government continually increases the economic pressures on our profession.

One response has been increased political activity. This is not unreasonable since politics is the mechanism used by human beings to deal with and create societal pressures. Unfortunately, many physicians are not political by nature and seem to lack the talent required for political success.

There was a time when excellence in our profession was a sine qua non for election to positions of power and responsibility. Furthermore, the physicians who were offered and accepted these responsibilities saw themselves as representatives of the profession, not of political constituencies and interest groups. Now, few physicians perceive the hospital position of Chief of Staff or Chief of Medicine as a position of honor. The result: politics as an end in itself, politics for self-aggrandisement, and politics without courage or leadership.

Professionalism—A Moderating Influence

A profession is, according to Webster, "the whole body of persons engaged in a calling requiring specialized knowledge and often long and intensive preparation." The connotation is that this body of persons shares not only specialized knowledge but a strong ethic. This ethic demands excellence measured in respect to that profession's purpose. It is the responsibility of that profession to demand of its members fidelity to its purpose and adherence to its code of ethics. These qualities must have a higher priority than the self-interest of the individual members of this body.

Unfortunately, we are significantly out of balance because we have lacked the leadership to successfully demand this kind of sacrifice from our profession. Perhaps organized medicine has failed the test of courage and has degenerated into political organizations designed solely to protect economic self-interest. Quality assurance to some means merely to get patients out of hospital promptly so as to protect profits. Few organizations have made any attempt to deal with the issues of maintaining quality and humanity, and their efforts might be described as at best marginally successful.

Some of you may agree that these truly are difficult times that cannot be ignored. How can we be optimistic when our nation is more deeply in debt than it has ever been and, even worse, goes more in debt every day? Other countries are making the cars we drive, the clothes we wear, and more recently the parts of our massive military machine on which we spend much of our nation's budget. Where is there room for good cheer when every patient has to be regarded as harboring a possible lawsuit, when we have more and more governmental laws and regulations to deal with, and where there is an excess of physicians?

A. N. Whitehead said,

> The middle-class pessimism over the future of the world comes from a confusion between civilization and security. In the immediate future there will be less security than in the immediate past, less stability. It must be admitted that there is a degree of instability—which is inconsistent with civilization. But, of the whole, the great ages have been unstable ages.

He made these remarks before World War I, and they still

apply today. So rejoice in that these are tumultuous times, for we are still in medicine's great age.

In spite of the perceptions of imbalance that make up this rather dire description of the state of our profession, we remain optimistic about the future, because of our long history of concern for the well-being of our patients and our desire for excellence. Although in a period of moderation now, the yang will return to achieve its rightful balance.

This will come about because a significant change is occurring in organized medicine. Just as the ascendency of the yin began with a political change within the American Medical Association in the 1930s, so will the ascendency of the yang occur as new leaders emerge unfettered by the preconceptions of the past.

Poison Control

FOR GASTROINTESTINAL DECONTAMINATION, the method that we recommend with respect to a sequential approach, is, first and foremost, the administration of activated charcoal. It doesn't exactly taste bad, because the stuff really has no taste. It's like having a wad of year-old peanut butter stuck to the roof of your mouth. We find that instead of eating activated charcoal with a spoon, if you can get a fairly dilute suspension, it goes down relatively easily because the patients tend not to get the big lumps trapped in around their tonsils.

Studies have shown that if you start out with an appropriate dose of activated charcoal and administer that about 20 minutes before gastric lavage, you can actually double what you're going to recover with gastric lavage.

Another advantage of using charcoal before lavage is that after you've used activated charcoal, you can always tell when the stomach is finally empty. When the aliquots of lavage fluid stop coming back black as midnight, you know that the stomach is pretty much as empty as it's going to be. Then, you can go ahead with the additional administration of activated charcoal, followed, of course, by the use of pulse charcoal.

By and large, just looking at the figures from a variety of studies that have been done, we can probably decrease absorption or recover up to 70% or even 80% of an ingested dose of medication if we are able to establish these gastrointestinal decontamination techniques on a timely basis. If we can do that, we are going to remove two to three times what we've ever been able to remove with the old method of using syrup of ipecac.

—MICHAEL V. VANCE, MD

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Why Isn't Every Woman Over 40 in a Breast Cancer Detection Program?

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Mortality from breast cancer may be reduced by more than 10,000 deaths per year in this country if the recommendations for screening all asymptomatic women older than 40 years for breast cancer, issued in 1982 by the American Cancer Society and the American College of Radiology, are followed. Compliance with those recommendations six years later is poor, even in well-to-do, medically served populations, primarily because of poor compliance by physicians. Radiation risk is an often-cited concern, although it has been shown to be an insignificant factor in breast cancer screening. High cost, also cited as a concern, is less of a problem—the charges for mammography having declined steeply in the past few years. At the current price levels, it makes financial and humanitarian sense to provide screening rather than terminal care for metastatic breast cancer. The third concern cited by physicians, that of diagnostic accuracy, must be addressed by a careful and accurate statistical description of the results of each screening program. Sensitivity of more than 80% with positive predictive values of about a third can be achieved.

(Robertson CL: Why isn't every woman over 40 in a breast cancer detection program? West J Med 1988 Jul; 149:111-112)

Reports of clinical mammography first appeared in this country more than 50 years ago.[1] The use of the technique, however, remained sporadic for many years because of such drawbacks as the high radiation dose to the breast, manual developing of the x-ray film, and difficulty in duplicating breast compression and positioning.

Following technical improvements in the method, two major studies of mammography were done. In 1963 the Health Insurance Plan Study compared two groups of women over a ten-year period and found a 30% reduction in cancer mortality among screened patients.[2] The second study was jointly sponsored by the American Cancer Society and the American Cancer Institute. Known as the Breast Cancer Detection Demonstration Program (BCDDP), it started in 1973 and involved 29 centers throughout the country, including the Boise Breast Cancer Detection Center (BCDC). The study showed that a major improvement in mammographic equipment and interpretive accuracy had occurred since the Health Insurance Plan Study ten years earlier. The BCDC study also proved that breast screening and the early detection of breast cancer were feasible in this country.[3]

Subsequently, studies in Holland and Sweden showed reductions in breast cancer mortality from 30% to 70% in a screened population.[4-6] Considering that each year in this country 120,000 new cases of breast cancer are detected and nearly 40,000 patients die of breast cancer, a reduction of 30% to 70% in mortality is highly desirable and would be of great significance in a disease expected to strike 10% of the female population of this country.[7]

By 1982 the case for breast cancer screening was so convincing that both the American Cancer Society and the American College of Radiology published guidelines for screening asymptomatic patients for breast cancer (Table 1).[8]

While differences in the two policies exist, both groups recommended that all women should have a baseline mammogram by age 35 to 40 and routine screening yearly after age 50.

Current Compliance With Screening Recommendations

A survey of middle-class women in Ann Arbor, Michigan, who were otherwise receiving medical care showed that fewer than 10% of asymptomatic patients were being screened by mammography in 1985.[9] In 1986, of 4,200 physicians in Los Angeles, only 11% reported compliance with the American Cancer Society's guidelines concerning breast cancer.[10] In a recent survey of patients receiving mammograms in the Midwest, only 50% of patients were referred for screening purposes. During the month covered by that survey, each physician referred only one to five patients for screening out of his or her entire patient population. Obviously, physician compliance with the established screening recommendations is extremely poor in this country, even in the best of circumstances.

Factors in Failure to Screen for Breast Cancer

The study of Los Angeles physicians cited various combinations of reasons for physicians' noncompliance with the published guidelines.[10] A combination of high cost and low yield was the leading factor for 55% of physicians, while 17% also included radiation hazard among the deterrents. Radiation hazard was the only concern for 7%, while another 7% believed that other screening modalities were adequate. The study found a clear correlation between compliance and the age of a physician: those younger than 40 were much more likely to encourage screening mammography.

Financial expense represents the greatest single problem in breast cancer screening, in my opinion, although charges have declined significantly over the past few years. For example, charges of more than $100 per mammogram were common until recently. Charges for screening mammog-

From the Breast Cancer Detection Center, Boise, Idaho.
Reprint requests to Charles L. Robertson, MD, 2309 Claremont Dr, Boise, ID 83702.

ABBREVIATIONS USED IN TEXT

BCDC = Breast Cancer Detection Center
BCDDP = Breast Cancer Detection Demonstration Program

raphy have been reported to range from $27 to $50 in the past two years.[11,12] The total charge at the Boise BCDC is $47, which includes the mammographic study and its radiographic interpretation, training in breast self-examination, breast examination by a skilled nurse practitioner, and inclusion in an ongoing study of breast cancer detection rates and accuracy. Aside from the obvious humanitarian benefits of the early diagnosis and treatment of breast cancer, it is also known that the financial cost of the early diagnosis of breast cancer by mammographic screening is lower than the cost of terminal care for patients dying of the disease.[13]

Radiation risks became a national issue in the early years of the BCDDP, when concern was expressed over the potential carcinogenic effect of irradiation of the breast in younger women. That debate proved to be valuable by stimulating all concerned to do two things. First, radiation doses were greatly reduced by the advent of improved equipment, films, and processing techniques. The average glandular dose was reduced from about 1.0 rad per examination to less than 0.3 rad at the current time. Second, the risks posed by irradiation of the breast tissue were carefully evaluated. Those studies have shown that, in comparative statistical terms, the radiation risk of the two-view mammographic study is considerably lower than the risks of traveling 60 miles by automobile, smoking three quarters of a cigarette, or being a 60-year-old woman for 20 minutes.[14] Therefore, radiation risks of mammography are thought to be an insignificant factor in breast cancer screening at this time.

The accuracy of mammography is a relatively confusing topic in the world literature for several reasons. First, many of the studies quoted are several years old, while mammographic techniques have been greatly improved in recent years. Second, many mammographic screening programs lack an aggressive long-term follow-up procedure to allow reliable calculation of accuracy figures. Therefore, many authors cite anecdotal evidence or guess at their own accuracy quoting series published by expert mammographers, despite the well-known wide variation in mammographers' accuracy. Third, inappropriate statistical measures of mammographic accuracy are often used.

In my opinion, a careful and well-documented follow-up procedure including a large number of patients over several years should be observed by each mammographer. The two statistical measures that best describe the efficacy of a screening program are sensitivity and positive predictive value. Sensitivity is the percentage of all patients found to have breast cancer within one year of screening who were correctly diagnosed as having breast cancer at the screening session. Separate figures for mammography and for physical examination findings can be calculated. The positive predictive value is the percentage of all biopsies done as a result of screening that resulted in the diagnosis of cancer.

Obviously, both numbers must be accurate and available to determine the accuracy of each mammographer. For example, a high sensitivity would be achieved at the expense of a low positive predictive value if every patient had a biopsy. Conversely, if biopsies were done only in patients with large, obvious cancers, the positive predictive value would be high, at the expense of sensitivity. A study of 40,318 patients from Stockholm, published in 1986, attained a sensitivity of 86% with a positive predictive value of 27%.[15] The first results of the Canadian National Study—also reported recently—include a sensitivity of 69% (range, 60% to 78%) and a positive predictive value of 8.6% (range, 3% to 16%).[16] The figures for the Boise BCDC are based on a follow-up greater than 80% at one year (Table 2).

TABLE 1.—*Summary of Guidelines for Detection of Breast Cancer in Asymptomatic Women*

Age, yr	*American Cancer Society*	*American College of Radiology*
20-34	BSE monthly; BPE every 3 yr	BSE instruction
35-39	Baseline mammogram; BPE every 3 yr	Baseline mammogram; BPE annually
40-50	Mammography every 1 or 2 yr; BPE annually	
Over 50	Mammography and BPE annually	

BSE = breast self-examination; BPE = breast physical examination

TABLE 2.—*Sensitivity and Positive Predictive Values for the Boise Breast Cancer Detection Center*

	1985	*1986*
Patients screened, No.	7,327	8,373
Cancers detected, No.	64	57
Sensitivity, %	83	84
Positive predictive value, %	32	34

Ancillary Screening Modalities

It would be ideal to develop a screening modality that is inexpensive, carries no radiation risk, and attains sensitivity and positive predictive values of 100%. Thermography, ultrasonography, and light transillumination studies are other screening modalities that have been tried. At the present time, none of these techniques are an adequate screening tool, and none are recommended for that purpose.

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Information

Nd:YAG Laser Therapy in Pulmonary Medicine

JAMES H. HARRELL II, MD
San Diego

In the past five years there has been a proliferation of multiuse medical lasers, such as the carbon dioxide, argon, and neodymium yttrium-aluminum-garnet (Nd:YAG). The CO_2 laser is in widespread use in otolaryngology, neurosurgery, dermatology, and gynecology. The argon laser is used in gastroenterology (particularly for superficial mucosal vascular lesions), dermatology, cardiology (for use with coronary arteries and other vessels), and pulmonary medicine in conjunction with hematoporphyrin derivatives.[1] The Nd:YAG laser is the most recent addition to this armamentarium and, because of its unique characteristics, it is particularly suited for use in pulmonary medicine. The principal characteristics of these three lasers are given in Table 1.

History of the Nd:YAG Laser

The introduction of the Nd:YAG laser to pulmonary medicine can be credited to the pioneering work of Dumon and co-workers in Marseilles, France.[2] Their group has established an impressive record for both safety and efficacy in more than 1,400 cases, has guided development of the instruments and techniques of therapy, and has actively taught the techniques to chest physicians throughout the world.

What makes the Nd:YAG laser useful in pulmonary therapy is its ability to coagulate and oblate; it is not as precise a cutting tool as the CO_2 laser.

Indications

The principal use for the Nd:YAG laser is for removing lesions obstructing the tracheobronchial tree[3] in patients who have symptoms of cough, bleeding, obstruction, infection, or shortness of breath. This obstruction may be due either to tumor, scarring, or other obstructing lesions, usually in patients who are not candidates for operative resection; the laser may be used before the patient has radiation therapy.

The extent of local anatomic extension of a tumor to be treated—its biologic behavior—is more important than its cell type, including even oat cell, when combined with irradiation or chemotherapy. Other well-accepted indications for using the Nd:YAG laser include

- Tumors of an uncertain prognosis such as adenoid cystic carcinoma or carcinoid in patients who do not fit the usual operative criteria, or to stabilize a patient before definitive resection;
- Metastatic disease to the bronchus when the primary disease is under good control;
- Granulation tissue;
- Sutures;
- Foreign bodies; and
- Papillomas.

Laser therapy may also be applied to benign strictures of the subglottic area, trachea, and main-stem bronchi with some success. It appears to work best when the stricture is due to either fresh granulation tissue or small tracheal webs not associated with more than one or two rings of cartilaginous destruction. Nd:YAG laser therapy may be definitive or may spare such patients intubation or a tracheostomy before a definitive operation.

The characteristics of airway lesions that indicate favorable and unfavorable responses to laser therapy are shown in Table 2.

Laser Safety

Laser therapy is several orders of magnitude more difficult and complicated than any routine bronchoscopic procedure. It is important that physicians undertaking this form of therapy be well trained in bronchoscopy and have a wide experience in recognizing intraairway lesions and in managing emergencies of the airway.[4] It is mandatory that they obtain the necessary experience with this modality, both didactic and "hands-on," at a center that is actively engaged in such a program.

Laser surgical therapy should only be done in an operating room or a specialized treatment room, although there is general agreement that surgical standby is not necessary. A team that includes an anesthesiologist and nurses is essential for success. Arterial oxygen saturation monitoring by ear or finger oximetry is mandatory, in addition to monitoring vital signs and electrocardiographic tracings; in selected cases, a Swan-Ganz catheter is necessary.[5]

The type of instruments used is particularly important. A special rigid bronchoscope is the instrument of choice unless

TABLE 1.—*Medical Lasers*

Type	*Wave Length, μm*	*Penetration Depth, mm*	*Delivery System*
Argon	0.5	1.0	Fiber-optic
Nd:YAG	1.06	4.0	Fiber-optic
CO_2	10.6	0.1	Mirror

TABLE 2.—*Types of Tissue and Their Responses to Laser Therapy*

Favorable Response	*Unfavorable Response*
Endobronchial lesion	Total airway obstruction
Intraluminal lesion	External airway compression
Polypoid lesion	Airway obstruction longer than 4 cm
Visible lumen	Lobar or segmental lesions in upper lobes
Short length of airway obstruction	Tracheal stenosis of bottleneck (hourglass) type
Lesion confined to trachea and main-stem bronchi	
Functional lung distal to obstruction	
Concentric tracheal stenosis	

(Harrell JH II: Nd:YAG laser therapy in pulmonary medicine. West J Med 1988 Jul; 149:113-114)

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there is a strong medical contraindication. A Dumon-Harrell scope is ideal in that it creates an airway, is not flammable, and can be used as a dilator or to bypass an obstruction to establish an airway. It has a major advantage of allowing suctioning and lasering at the same time. Large pieces of tissue can be removed easily through the channel, and closed-system ventilation is possible when necessary.

Techniques

The procedure is ideally done with the patient under a general anesthetic, with appropriate monitoring as outlined above. The anesthetic agent chosen must be nonflammable. In our hands, isoflurane after induction with thiopental sodium (Pentothal), along with topical tetracaine with epinephrine, has proved useful. Packing is placed around the rigid scope, and petroleum jelly-saturated gauze is applied to the nostrils. The inspired concentration of oxygen is maintained at between 40% and 45%. During the laser procedure, the patient is allowed to breathe spontaneously. It is important that an appropriate power setting be applied; usually 40 to 50 watts for half a second is adequate to remove any tumor. The fiber-optic scope can be placed through the rigid scope for pulmonary lavage. This is indicated when the oxygen saturation decreases due to airway obstruction by blood or other material. Lavage is also necessary to reach areas that cannot be seen with the rigid scope.

Bleeding remains the major complication—usually unavoidable—of laser therapy; significant bleeding can flood the tracheobronchial tree and cause arterial hypoxemia. Other complications include airway perforation, a tracheoesophageal fistula, fire, and scope damage. Fire and scope damage are usually the result of poor training techniques.

Contraindications and Benefits

Contraindications to laser therapy include a bleeding diathesis; terminal, diffuse metastatic disease; a tumor location incompatible with resection (the distal tracheobronchial tree); and some areas of complete obstruction in which inadequate landmarks are present. Lesions of the left bronchial tree must be approached with care because of the proximity of the major vessels.

The possible benefits of laser therapy are that it can provide immediate relief of airway obstruction with resultant improved ventilation, it can be a means of stopping tumor bleeding, and it can help to establish drainage in patients with infection due to airway obstruction. In selected patients, laser intervention can offer immediate improvement in their quality of life and performance status. It can shorten their hospital stay, and, in certain selected cases, the procedure can be done on an outpatient basis. Most patients can be evaluated and successfully treated in two to three days. In our experience with more than 500 patients with lung tumors and other forms of airway obstruction, there was a single major complication with a fatal hemorrhage, as exophytic tumor was removed that made up the wall of the right middle lobe artery. There have been three postoperative deaths due to progressive respiratory insufficiency in patients who were eventually found to have lesions that could not be totally removed.

The Future of Nd:YAG Laser Therapy

The current instruments will probably remain "state-of-the-art" for the next three to five years. The fibers are still the vulnerable part of the instrument, and they are most likely to deteriorate with continued use. The use of lasers will have an increasing role as an adjuvant form of therapy in patients with malignant tumors that are causing high-grade obstruction. The goal of such therapy should be to improve the patient's overall well-being and performance status. Laser therapy will also have an increased role in managing benign conditions such as tracheal stenosis and papillomas.

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Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists

Precautions: *General*—1 Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy

2 Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency

3 Pharmacokinetic studies in patients with hepatorenal syndrome have not been done Part of the dose of nizatidine is metabolized in the liver In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects

Laboratory Tests—False-positive tests for urobilinogen with Multistix* may occur during therapy with nizatidine

Drug Interactions—No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system, therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b i d , was administered concurrently

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement compared to concurrent controls, and evidence of mild liver injury (transaminase elevations) The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus There are, however, no adequate and well-controlled studies in pregnant women It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating rats Pups reared by treated lactating rats had depressed growth rates Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers

Pediatric Use—Safety and effectiveness in children have not been established

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups Age alone may not be an important factor in the disposition of nizatidine Elderly patients may have reduced renal function

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0 2%), urticaria (0 5% vs <0 01%), and somnolence (2 4% vs 1 3%) were significantly more common in the nizatidine group A variety of less common events was also reported, it was not possible to determine whether these were caused by nizatidine

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU/L The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients All abnormalities were reversible after discontinuation of Axid

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo Rare reports of gynecomastia occurred

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist On previous occasions, this patient had experienced thrombocytopenia while taking other drugs

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported.

Overdosage: There is little clinical experience with overdosage of Axid in humans If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy Renal dialysis for four to six hours increased plasma clearance by approximately 84%

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal Intravenous LD_{50} values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively PV 2091 AMP [041288]

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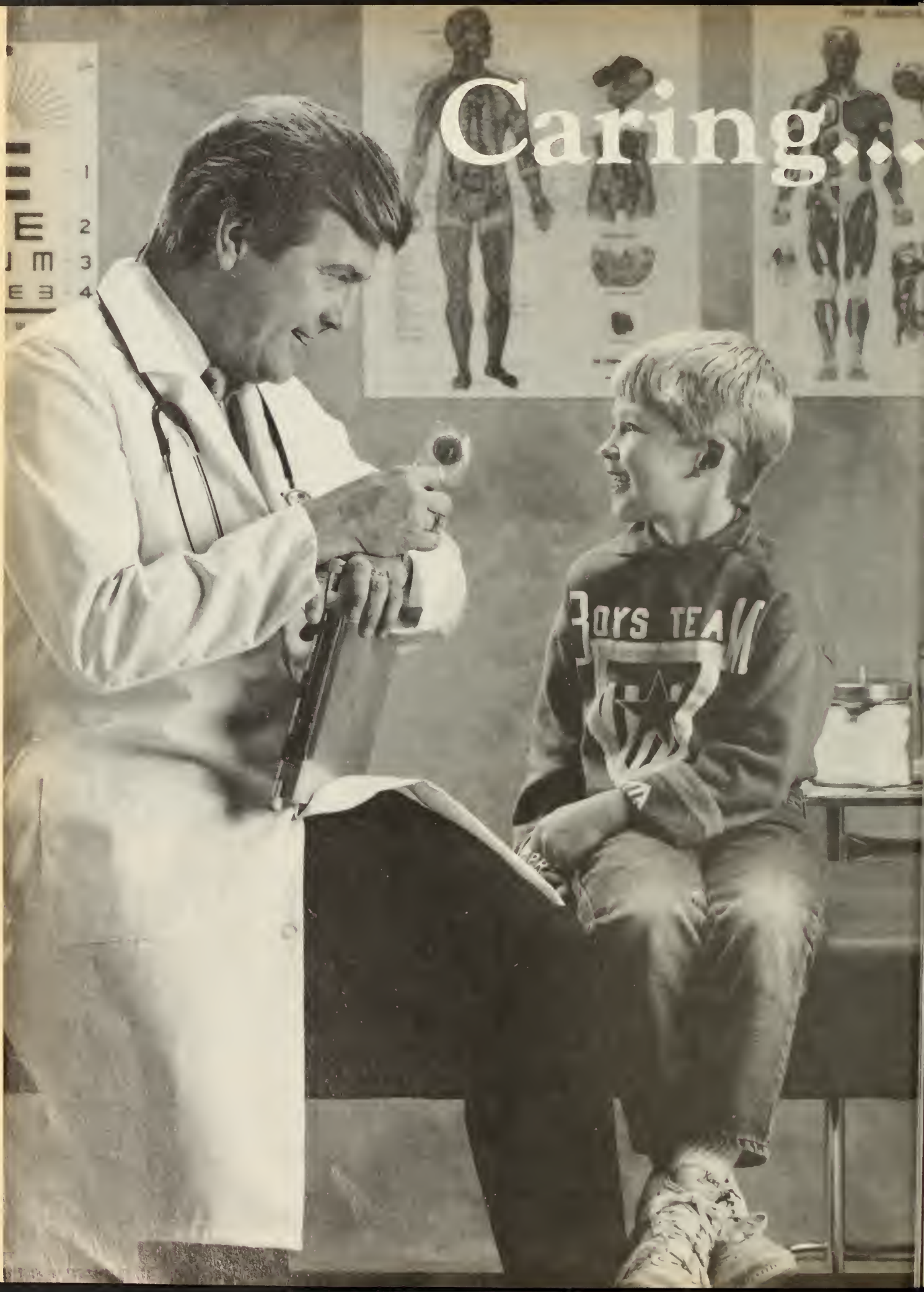

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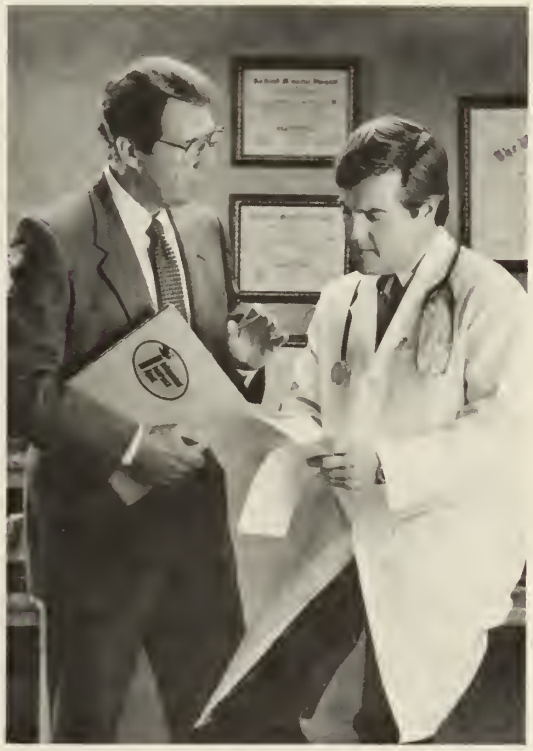

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CONTINUING MEDICAL EDUCATION

(Continued from Page 34)

INTERNAL MEDICINE

August 1-5—**Internal Medicine—36th Annual Update and Board Review.** USC at Health Sciences Campus, Los Angeles. Mon-Fri. 38 hrs. $295. Contact: USC.

August 21-26—**New Advances in Internal Medicine: Clinical Applications.** UCD at Hyatt Regency, Monterey. Sun-Fri. 23 hrs. $410. Contact: UCD.

September 15-18—**Medical Acupuncture for Physicians: Part I.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. Thurs-Sun. 200 hrs. $3,200. Contact: UCLA.

September 22-24—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. Contact: Dr Luis M. de la Maza, Department of Pathology, Rt 84, UCI Medical Center, 101 City Drive S., Orange, 92668. (714) 634-6868.

October 4-7—**Rheumatology and Clinical Immunology.** UCSF at Stanford Court, San Francisco. Tues-Fri. 19 hrs. $395. Contact: UCLA.

November 3-5—**New Directions in Anti-viral Chemotherapy.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. $100. Contact: UCSF.

November 7-9—**12th Annual Cancer Symposium.** Scripps Memorial Cancer Hospital at Sheraton Harbor Island Hotel E, San Diego. Mon-Wed. 21 hrs. $390. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

December 1-2—**Recent Advances in Occupational Cancer.** UCSF at Hotel Meridien, San Francisco. Thurs-Fri. $220. Contact: UCSF.

December 30-January 8—**Medical Acupuncture for Physicians: Part II.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. 10 days. 200 hrs. $3,200. Contact: UCLA.

January 6-7—**6th Annual Reider Laser Symposium—Urology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

OB/GYN

August 19-21—**1988—Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates and San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

November 10-13—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sat. Contact: UCI.

November 12—**Infertility Update V.** Scripps Clinic and Research Foundation Amphitheater, La Jolla. Sat. 7 hrs. $110. Contact: Bonny Mower, Box 400S, Dept of Academic Affairs, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

November 13-19—**11th Annual Review Course in Clinical Obstetrics & Gynecology.** The Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

January 6-7—**6th Annual Reider Laser Symposium—Gynecology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

PEDIATRICS

August 22-24—**Pediatrics Update: 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 15-20—**American Academy of Pediatrics Annual Session.** AAP. Sat-Thurs. Contact: AAP, 1801 Hinman Ave., Evanston, IL 60201.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

December 3—**7th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Educational Center, San Diego. Sat. 7 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 10-12—**Current Concepts in Pediatric Medicine.** Children's Hospital & Health Center at Marriott Hotel, San Diego. Wed-Fri. Contact: Children's Hospital & Health Center, Continuing Medical Education Office, 8001 Frost St, San Diego 92123. (619) 576-4072.

PSYCHIATRY

August 24-29—**The Neuropsychiatric Aspects of Politics and Politicians.** Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, Hawaii. Wed-Mon. 24 hrs. Contact: Barbara Harwell, SCNPI, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

November 18-20—**34th Annual Group Therapy Symposium.** UCSF. Fri-Sun. Contact: UCSF.

RADIOLOGY

July 16-17—**Two-Day Seminar in Breast Imaging with Interpretive Workshops.** Los Angeles Radiological Society at Registry Hotel, Universal City. Sat-Sun. 10 hrs. $200. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

July 28-31—**Second Annual Symposium on Magnetic Resonance Imaging.** Hoag Memorial Hospital at Ritz-Carleton Hotel, Laguna Niguel. Thurs-Sun. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 1-5—**Modern Radiology Practice.** UCSD at Fess Parker Red Lion Resort, Santa Barbara. Mon-Fri. 30 hrs. $425. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

August 22-26—**Radiology: 1988 USC Radiology Summer Hawaiian Seminar.** USC at Kauai Westin, Lihue, Hawaii. Mon-Fri. 28 hrs. $475. Contact: USC.

August 25-28—**Fourth Annual Physics and Biology of Radiology.** UCSD at La Jolla Village Inn. Thurs-Sat. 25 hrs. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 9-11—**Fourth Annual Sonography Update and Review Course.** UCSD at Hanalei Hotel, San Diego. Fri-Sun. 17 hrs. $375. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

October 31-November 1—**San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronada, San Diego. Mon-Tues. 28 hrs. $450. Contact: UCSD.

December 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 13-15—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: R. Dawne Ryals, PO Box 920113, Norcross 30092-0113. (404) 641-9773.

SURGERY

July 30-August 6—**Clinical Problems in External Disease and Anterior Segment Surgery.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. 1 week. 26 hrs. $535. Contact: USC.

August 18-21—**Discussions of Current Hand Care Concepts.** Plastic Surgery Education Foundation at San Diego. Thurs-Sun. Contact: PSEF, 233 N. Michigan Ave, Suite 1900, Chicago, Illinois 60601.

August 28-31—**Under Pressure II: Glaucoma 1988.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Wed. 12 hrs. $335. Contact: UCD.

September 16—**Ultrasonic Liver Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Fri. 8 hrs. Contact: UCD.

September 17—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

October 3-7—**6th Annual Comprehensive Review of Vascular Surgery.** UCLA Miramar Sheraton, Santa Monica. Mon-Fri. 32 hrs. $595. Contact: UCLA.

(Continued on Page 120)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 118)

October 12-14—**Hip and Knee Reconstructive Surgery 1988.** UCLA at Sheraton Princeville Hotel, Kauai, Hawaii. Wed-Fri. Contact: UCLA.

October 14-15—**13th Annual Clinical Neurosciences Symposium.** Dominican Neurologic Institute at Chaminade Conference Center, Santa Cruz. Fri-Sat. 11 hrs. $350. Contact: Karen Rickenbach, DNI Dominican Hospital, 1555 Soquel Dr, Santa Cruz 95065. (408) 462-7562.

December 3—**Reider Laser YAG & Argon Laser/Brachytherapy Symposium.** Center for Health Education, Long Beach. Sat. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

December 3—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

December 3—**Cleft Palate Symposium.** UCD at Hyatt Regency Hotel, Sacramento. Sat. Contact: UCD.

OF INTEREST TO ALL PHYSICIANS

July 15-18—**Caring for People With AIDS and Their Loved Ones.** Concern for Dying: an Educational Council, at Bishop's Ranch, Healdsburg. Fri-Mon. Contact: Penny Weingarten, 250 West 57th St., Room 831, New York, NY 10107. (800) 248-2122.

July 16-18—**Laboratory and Clinical Aspects of Microbiological Diagnosis.** UCLA at Hotel Le Meridien, Newport Beach. Sat-Sun. Contact: UCLA.

July 18-21—**12th Annual Selected Topics for Primary Care Physicians.** LLU. Mon-Thurs. Contact: LLU.

July 25-29—**SPORTS MEDICINE 1988: A Practical Approach to Caring for Today's Athletes.** UCSD at San Diego Princess. Mon-Fri. 23 hrs. Contact: UCSD.

July 27-31—**Wilderness Medicine '88.** Wilderness Medical Society at Squaw Valley, Lake Tahoe. Wed-Sun. 22 hrs. Contact: Jackie Silva, Coordinator, Mountain Medical Seminars, PO Box 321, Yreka, 96097. (916) 842-4667.

August 1-3—**4th International ND: YAG Laser Symposium.** International Laser Foundation at Sheraton Universal Hotel, Los Angeles. Mon-Wed. Contact: ILF, 3960 Park Blvd, Ste E, San Diego 92103. (619) 692-9115.

August 3-6—**15th Annual Meeting: The Peruvian American Medical Society** at Westin Bonaventure Hotel, Los Angeles. Wed-Sat. Contact: Hugo Ortiz, MD, Chairman, Scientific Program, 6488 Tamerlane Dr, West Bloomfield, MI 48322.

August 12-14—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Doubletree Inn, Monterey. Fri-Sun. $225. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

August 13-20—**8th Annual Symposium on Fine Needle Aspiration.** UCSF at Kaanapali Beach, Maui. 1 week. 25 hrs. Contact: UCSF.

August 14-24—**31st Anniversary Postgraduate Refresher Course.** USC at Sheraton Waikiki and Westin Kauai, Hawaii. Sun-Wed. 42 hrs. $535. Contact: USC.

August 17-27—**31st Anniversary Postgraduate Refresher Course.** USC at Sheraton Waikiki and Westin Kauai, Hawaii. Wed-Sat. 41 hrs. $535. Contact: USC.

August 18-19—**7th Annual Symposium: General Medicine Update for Practicing Physicians.** Northern Inyo Hospital, Bishop. Thurs-Fri. 10 hrs. Contact: Lynda Schmidt, Northern Inyo Hospital, 105 Pioneer Lane, Bishop 93514. (619) 873-5811.

August 21-31—**31st Anniversary Postgraduate Refresher Course.** USC at Westin Kauai and Mauna Kea, Hawaii. Sun-Wed. 41 hrs. $535. Contact: USC.

August 26-28—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel Coronado Island, San Diego. Fri-Sun. 18 hrs. $225. Contact: Bonny A. Mower, Dept of Academic Affairs, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

September 8-10—**New Advances in Common Neurologic Disorders.** UCSD Division of Neurology at Catamaran Resort Hotel, San Diego. Thurs-Sat. 14 hrs. $300. Contact: Shirley Kolkey, Conference Coordinator, 3770 Tansy, San Diego 92121. (619) 453-6222.

September 15-18—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

September 16-17—**AIDS: A Practical Program Designed for Community Based Physicians.** UCD at Hyatt Regency Hotel, Sacramento. Fri-Sat. Contact: UCD.

September 17—**Treatment Issues With Adult Children of Alcoholics and Co-Alcoholics in Group and Individual Therapy.** Institute for Addiction Studies at Health Education Center, Oakland. Sat. $55. Contact: Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave, Oakland 94609-3081. (415) 652-7000.

September 24—**Lumbar Spine Disease: A Practical Approach for the Primary Care Practitioner.** Scripps Clinic and Research Foundation at Amphitheater, La Jolla. Sat. 5 hrs. $50. Contact: Bonny A. Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

September 28-30—**Primary Care Medicine: Principles and Practice.** UCSF at the Portman Hotel, San Francisco. Wed-Fri. $365. Contact: UCSF.

October 10-14—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 11-14—**Intervention Training.** Monterey Community Hospital Recovery Center, Monterey Conference Center. Tues-Fri. $250. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

October 15-18—**Infectious Diseases: Part I of II.** EPIC Expeditions at Napa Valley. Sun-Tues. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 19-22—**Infectious Diseases: Part II.** EPIC Expeditions at Sonoma Valley. Wed-Sun. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 20-22—**What the Clinician Should Know About the Treatment of Chemical Dependence: A Review and Update for Physicians.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at Los Angeles Airport Marriott. Thurs-Sat. 19 hrs. $350. Contact: Gail Jara, California Society. 3803 Broadway, Oakland 94611. (415) 428-9091.

October 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 21-23—**Office Orthopaedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, Medical Education, PO Box 84296, San Diego 92138. (619) 223-2997.

October 25—**Sexual Addiction and Chemical Dependency: The Hidden Connection.** Institute for Addiction Studies at Health Education Center, Oakland. Sat. $55. Contact: Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave, Oakland 94609. (415) 652-7000.

October 27-30—**Clinical Nutrition.** UCD at Sonoma Valley. Thurs-Sun. Contact: UCD.

October 31-November 3—**Intervention Workshop.** McDonald Center for Alcoholism and Drug Addiction Treatment at La Valencia Hotel, La Jolla. Mon-Thurs. 27 hrs. $250. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

November 4-5—**UCD Multi-Specialty Update: Medical Advances of the 80's.** UCD at Sacramento. Fri-Sat. Contact: UCD.

November 10-13—**Sexual Literacy: What is it? What do we know? What do we need to know? Whose responsibility is it?** The Society for the Scientific Study of Sex at the Cathedral Hill Hotel, San Francisco. Thurs-Sun. Contact: Bernard Goldstein, San Francisco State University, Biology Dept., 1600 Holloway Ave., San Francisco, 94132. (415) 338-1548.

November 11-14—**The Spine: Current Concepts of Diagnosis and Treatment.** Spine Study Group at Marriott Desert Springs Resort, Palm Springs. Fri-Mon. $250. Contact: Spine Study Group, PO Box 33185, San Diego 92103. (619) 692-9115.

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November 16—**Common Musculoskeletal Problems.** Veterans Administration Medical Center, Sepulveda. Wed. 6 hrs. Contact: Arun J. Mehta, MD, Rehabilitation Medicine Service (117), VA Medical Center, Sepulveda 91343. (818) 891-2473.

January 19-22—**Health Science Response to Child Maltreatment: 1989.** Children's Hospital & Health Center at Omni Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

IDAHO

July 21-23—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

August 6-13—**Acute and Emergency Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. 24 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

August 29-30—**Northwest Regional Perinatal Conference—Current Issues in Ob/Gyn, Neonatology and Pediatrics.** Inland Empire Perinatal Center at Coeur d'Alene Resort. Contact: Inland Empire Perinatal Center, 411 Medical Center Bldg, Spokane, WA 99204. (509) 624-3182.

September 2-5—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. 12 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 18-21—**Ruidoso Family Practice Seminar.** Inn of the Mountain Gods, Mescalero. Mon-Thurs. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

July 22-24—**Diagnosis and Management of Arrhythmia.** Presbyterian Heart Institute, Albuquerque. Fri-Sun. Contact: Barry Ramo, MD, (505) 841-1065/(505) 242-2796.

July 28-30—**General Surgical Update.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

August 5-6—**Santa Fe Cardiology Update.** Fri-Sat. Contact: New Heart Program, (505) 255-8474.

September 8-10—**Concepts & Controversies in Perinatal Care.** Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

September 22-24—**Primary Care Update '88.** UNM Conference Center, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 6-8—**Management of Radiation Accidents.** Sheraton Old Town Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 7-8—**4th Annual Balloon Fiesta Lung Conference.** Fri-Sat. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

October 18-21—**Epidemiologic & Methodologic Problems in Determining Nutritional Status of Older Persons.** Sheraton Old Town Hotel, Albuquerque. Tues-Fri. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 28-29—**New Mexico Medical Society Interim Meeting** and **Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Journal Center Pyramid Holiday Inn, Albuquerque. Fri-Sat. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 11-13—**Adolescent Medicine.** Hilton Inn, Las Cruces. Fri-Sun. Contact: Marilyn Stark, NM Chapter, American Academy of Pediatrics, 7605 Mountain NE, Albuquerque 87110. (505) 265-7431.

December 1-3—**American College of Physicians—New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

December 9-10—**Trauma Update '88.** Clarion Four Seasons Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

February 24-26—**17th Annual New Mexico Thoracic Society Lung Disease Conference.** Taos. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 217 Truman NE, Albuquerque 87108. (505) 265-0732.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

August 13-15—**Retrieved Implants and Biomaterials** (Sponsor: UUMC). Fri-Sun. Contact: Rosalie Lammle, (801) 581-8664.

September 22-24—**Central Association of Obstetricians & Gynecologists** (Sponsor: UUMC). Thurs-Sat. 10.5 hrs. Salt Lake City Marriott. Contact: (801) 333-0988.

(Continued on Page 124)

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CRESCENT CITY, CALIFORNIA. Exciting position available at a growing 24,000 visit ER in a rural, coastal community. Fee-for-service with possibility of six figure income. Send CV to Art B. Wong, MD, FACEP, EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

FAMILY PRACTICE in four season playground. Live, work, and play in beautiful north Idaho. Excellent professional opportunity. Private practice affiliated with JCAH accredited hospital. For details call Nancy collect at (208) 784-1221, ext 304. Shoshone Medical Center, Jacobs Gulch, Kellogg, ID 83837.

CALIFORNIA, SONORA. Staff Physician position available in 11-12,000 visit ER in quaint, historic, growing gold country community with fantastic recreational opportunities, one hour from Yosemite. Excellent opportunity in an academic and democratic group. Send CV to Art B. Wong, MD, FACEP, EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

SOUTH CENTRAL WYOMING. Immediate practice opportunity for BC/BE Urologist. Well-equipped JCAH hospital for a service area of approximately 20,000 population. No state or city income tax. Relocation incentives. Superior hunting, fishing, camping, snowmobiling. Three hours to Colorado ski area, five hours to Jackson Hole. One and one-half hours to the mountains. If interested, please send CV and references to D. Abels, DO, Chairman, Recruiting Committee or Richard Mills, Executive Director, Memorial Hospital of Carbon County, Rawlins, WY 82301; (307) 324-2221.

PHYSICIANS WANTED

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

PHYSICIANS WANTED. A General Surgeon and an Oncologist to join 16 physician multispecialty group with attached 40-bed hospital located in southern Idaho. Contact Business Administrator, Box 1233, Twin Falls, ID 83301.

GENERAL PRACTICE. Busy medical center needs full-time physicians for urgent appointments. Significant evening and weekend hours. Abundant free time with no on-call responsibility. Excellent benefits and retirement program. Kaiser Permanente, Santa Teresa Hospital, 250 Hospital Pkwy, San Jose, CA 95119; (408) 972-6180.

FAMILY PRACTICE/GENERAL PRACTICE wanted for full-time practice to work three days a week and share with another Practitioner. Rural setting, good pay, nice people. Can commute for two nights a week, one hour Sacramento, one hour and 15 minutes Nevada City, two hours San Francisco. Contact Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

ONCOLOGIST/INTERNIST BC/BE wanted to join hospital-based multispecialty clinic near San Francisco. Complete benefit package. Send résumé to Gary Hillman, MD, Chief, Department of Medicine, Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063; or call (415) 780-2626.

GENERAL SURGEON. Opportunity for BC/BE Surgeon with fellowship or experience in Vascular Surgery to join Surgeon in active practice in southeastern Washington state; well-equipped 71-bed hospital undergoing expansion. Send current CV to J. Griffith, PO Box 6128, Kennewick, WA 99336.

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PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St Southwest, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

WASHINGTON. Excellent opportunity for caring BC/BE physician to join a 35 member multispecialty clinic as the second physician in our expanding facility based Immediate Care Department. Competitive salary and generous fringe benefits including paid education leave, vacation, insurance, and retirement. Send inquiries and CV to R. G. Caudill, MD, Walla Walla Clinic, 55 W. Tietan, Walla Walla, WA 99362.

PHYSICIANS WANTED. We have full and part-time locum tenens opportunities available with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM, Atlanta, GA 30346; 1 (800) 544-1987.

GENERAL INTERNIST needed for large hospital-based multispecialty clinic. University associated residency program. Attractive salary and complete benefit package. Pleasant setting. BC/BE. California license required. Contact Dennis L. Ostrem, MD, Chief Internal Medicine, The Permanente Medical Group, Inc, PO Box 254999, Sacramento, CA 95865-4999 or call (916) 973-5781. An Equal Opportunity Employer.

FAMILY PRACTITIONER. Busy four physician Family Practice group (including OB) seeks replacement for partner departing fall, 1988. Located in Alaska's capital city in the Tongass National Forest offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

PEDIATRICIAN, BE/BC, needed July 1988 in four-season playground. Excellent practice opportunity with positive financial success. Send CV to Dr Gerald E. Carlson, Women's Medical Clinic, 1203 10th St South, Nampa, ID 83651; (208) 467-2400.

OB/GYN, SEATTLE AREA. Rapidly growing practice seeks third OB/GYN. Come practice in a picturesque community on Puget Sound. Nearby mountains and lakes provide limitless recreational opportunities. University of Washington continuing education minutes away. For excellent incentive-oriented compensation and benefits contact Philip DuBois, MD, 7935 216th St SW, Ste E, Edmonds, WA 98020; (206) 775-0681.

ENJOY COUNTRY LIVING and outstanding year 'round outdoor recreation, excellent school system, clean environment! Join two BC Internists with growing practice in historical Wyoming community. We seek BE/BC Internist candidates recently trained or in university affiliated program. Income guarantee, paid malpractice and health insurance, more! Contact Cynthia Lacro, PRO-SEARCH, 305 NE 102nd Ave, Portland, OR 97220; 1 (800) 237-6906.

(Continued on Page 125)

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Pediatrics	7,357	2,365	68%	6,208	2,052	67%
Urology	18,571	13,735	26%	14,560	11,776	19%
Anesthesiology	19,704	13,735	30%	16,299	11,776	28%
General Surgery	30,841	17,853	42%	22,388	15,306	32%
Plastic Surgery	31,557	17,853	43%	22,961	15,306	33%
Orthopedic Surgery w/Spinal	39,744	21,971	45%	34,184	18,837	45%
Obstetrics/ Gynecology	49,812	21,971	56%	40,220	18,837	53%

* Insurance company composite rates are averages based upon 4/1/88 rates of The Doctors' Company, 6/1/87 rates of MIEC, 1988 rates of Norcal and SCPIE. Details of source data on request. No costs shown here for San Diego or Imperial County. Other surcharges, credits, reductions may apply. All costs based on mature rate (including retroactive coverage).

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(Continued from Page 121)

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

July 21-23—**Common Office Procedures.** Seattle. Thurs-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

July 22-24—**First International Symposium on Pediatric Pain.** Seattle. Fri-Sun. Contact: U/W, Maria Lilja, (206) 543-1050.

July 25-29—**Psychiatry for Primary Care: Joint Efforts to Aid Patients and Their Families.** Seattle. Mon-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

July 29-31—**Seafair Anesthesia X.** Seattle. Fri-Sun. Contact: VMMC.

August 1-5—**Postgraduate Seminar in Psychology: Modern Approaches to Psychological Interviewing.** Ellensburg. Mon-Fri. Contact: Central Washington University, (509) 963-2381.

August 5—**Otology Update.** Seattle. Fri. Contact: VMMC.

August 9-14—**Summer Seminar on Medical Ethics.** Whistler, BC. Tues-Sun. Contact: U/W, Maria Lilja, (206) 543-1050.

August 11-13—**Surviving the Elements.** Seattle. Thurs-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

August 29—**NW Regional Perinatal Conference: Current Issues in OB/GYN, Neonatology and Pediatrics.** Coeur d'Alene, Idaho. Thurs. Contact: (509) 624-3182.

August 31-September 3—**Second International Forum of Otorhinolaryngology.** Seattle. Wed-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

September 9—**Update on Anxiety and Depression.** Seattle. Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

September 12-16—**16th Annual Family Practice Review Course.** Seattle. Mon-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

September 17-24—**Effective Management of Common Sports Injuries.** San Juan Islands. Sat-Sat. Contact: Kathy Rairigh, EPIC Expeditions, (208) 788-4995.

September 22-24—**Orthopedic Biomechanics.** Seattle. Thurs-Sat. Contact: VMMC.

October 27-28—**Annual Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

WYOMING

June 23-26—**Wyoming Medical Society Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sun. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

July 16-23—**The Treatment of Infectious Diseases.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Yellowstone. 24 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

July 18-22—**6th Annual Update in Clinical Microbiology and Immunology.** University of Utah Medical Center at Jackson Hole. Mon-Fri. 25 hrs. Contact: UUMC, 50 N Medical Dr, Salt Lake City, UT 84132. (801) 581-2258.

July 23-30—**Up-to-date Pulmonary and Cardiac Medicine.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Jackson Hole and Yellowstone. 24 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

September 9—**Thrombolysis and Hemostatic Disorders.** West Park Hospital, Cody. Fri. Contact: Elaine Nestell, Education Director, West Park Hospital, 707 Sheridan Ave, Cody 82414. (307) 527-7501, ext 250, or 1 (800) 654-9447.

September 14-18—**Wilderness Medicine '88—Annual Meeting of the Wilderness Medical Society.** Jackson Lake Lodge, Grand Teton National Park. Wed-Sun. Contact: Diag Simpkins, Wilderness Medical Society, PO Box 397, Point Reyes Station, CA 94956. (415) 663-9107.

September 17-18—**Medicine Update.** Creighton University School of Medicine at Inn at Jackson Hole, Teton Village. Sat-Sun. 10 hrs. Contact: Division of CME, Creighton University School of Medicine, Omaha, NE 68178. (800) 548-2633. ◆

(Continued from Page 122)

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ENT PHYSICIAN, CALIFORNIA. BE/BC ENT to join staff of 14 physician multispecialty group located in the central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to William R. Winn, MD, Kaweah Medical Group, Inc., 222 West Willow St, Visalia, CA 93291.

WASHINGTON. Openings for career oriented Emergency Physicians, BC/BE in Emergency or Primary medical specialty. In a Seattle metropolitan hospital with 35,000 annual visits. Excellent salary with partnership potential in stable, growing group. Contact Beth Welsh at Valley Medical Center, 400 S. 43rd St, Renton, WA 98055.

PORTLAND, OREGON. Established, rapidly growing practice seeks BE/BC Internist. Multispecialty group active in private and HMO practice with satellite office. Salary and benefits first two years lead to partnership. Send CV to SMC, 10535 NE Glisan St, Portland, OR 97220, Attn: Dick Hamilton; (503) 256-0594.

FAMILY PRACTICE, PUGET SOUND. 23 physician multispecialty group is seeking Family Practitioner. Our facility has in-house lab and x-ray facilities and is conveniently located one block from Level III hospital. Attractive salary and benefits; partnership opportunity. Send CV to Carol Larsen, Acting Director, c/o The Western Clinic, PO Box 5467, Tacoma, WA 98405.

RHEUMATOLOGIST. Immediate opening for BC/BE Rheumatologist with large prepaid group practice in San Francisco bay area. Busy clinical practice with opportunities for teaching and research. University appointment possible. Competitive salary. Generous benefit package. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, Permanente Medical Group, 260 International Cir, San Jose, CA 95119, or phone (408) 972-6560.

FAMILY PRACTICE PHYSICIAN WANTED. Salt Lake area family practice clinic. Close to skiing and excellent outdoor recreational opportunities. Income guaranteed and excellent benefits. Contact Robert Davis, MD, Director, Family Medical Center, 1781 West 9000 South, West Jordan, UT 84088; (801) 562-9100.

CALIFORNIA

Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

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SACRAMENTO. BC/BE Family Physicians needed for full-time primary care clinic, part-time ER/part-time primary care clinic, or full-time in our ER. We are a large-staff model HMO offering competitive salary, excellent benefit package, and shareholder status. California license required. Contact Richard Fury, MD, 1001 Riverside Ave, Roseville, CA 95678 or call (916) 784-4620. EOE.

ASSOCIATE MEDICAL DIRECTOR. Excellent opportunity for BC physicians to become a part of the Medical Department of one of the largest utilization and case management corporations in the U.S. The company specializes in remote utilization review, and in managed medical care for corporate and insurance carrier clients coast-to-coast. There will be an opportunity to work with physicians and develop treatment plans and alternate treatment sites for patients on a nationwide basis. Opportunities for input into corporate programs and strategic planning also exist. Utilization review experience is preferred but not necessary. Specialty Board certification is required. Respond to Director, Medical Department, 3200 S. Highland Ave, Downers Grove, IL 60515-1223.

SAN FRANCISCO. Outstanding opportunity for BC/BE Internist, Family Practitioner, OB/GYN, or Orthopedic Surgeon at 260-bed community hospital in the dynamic South of Market area. Excellent opportunity to join busy, growing practices. Competitive salary and benefits package. Send CV to Walter Kopp, St. Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

ORTHOPEDIST, NEUROLOGIST, AND PHYSIATRIST one to two days per week for office-based practice specializing in evaluation and non-emergency treatment of traumatic injury patients. California license required. Medico-legal experience helpful. Fee for service, with high earning potential. CV to Director, PO Box 14046, San Francisco, CA 94114.

MONTANA. BC Family Practitioner seeks partner with interests in Obstetrics and Rural Medicine to join busy practice in southeast Montana. Office on hospital/NH campus. First year income guarantee, relocation assistance, and other benefits. Enjoy comforts of friendly small community living and recreation that only Montana can offer! Send CV to Cynthia Lacro, PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (800) 237-6906.

SURGERY, CALIFORNIA. BE/BC General/Thoracic Surgeon to join staff of 14 physician multispecialty group located in the central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to William R. Winn, MD, Kaweah Medical Group, Inc., 222 West Willow St, Visalia, CA 93291.

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INTERNIST. San Francisco-based growing practice BC/BE with or without subspecialty. CV to PO Box 640464, San Francisco, CA 94109.

CALIFORNIA, BERKELEY. Emergency physician group seeking physicians for full-time positions at community hospital-based urgent care center. Applicant must be at least two year post internship. Experience in primary care settings is required. Salary and work conditions are highly competitive. Contact Alta Emergency Medical Group, PO Box 1233, Berkeley, CA 94701.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Department at the University of California, Davis, Medical Center. The University serves a large region of northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff (240 per year) in addition to treating patients. Emergency Department physicians also provide medical control for UCDMC Life Flight, director of base station activities, and are actively involved in trauma care. Opportunities exist for involvement in other UCD School of Medicine teaching activities. Applicants should send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817

PHYSICIANS WANTED

PHYSICIANS WANTED IN TEXAS, OKLAHOMA, and ARIZONA. Cardiology, ENT, Family Practice, General Practice, General Surgery, Internal Medicine, OB/GYN, Orthopedic Surgery, Pediatrics, Psychiatry, Radiology. Excellent quality of life, first year guarantee, etc. Other opportunities available also. Reply with CV or call Armando L. Frezza, Medical Support Services, 8806 Balcones Club Dr, Austin, TX 78750; (512) 331-4164.

RESEARCH ASSISTANT/ASSOCIATE PROFESSOR of Medicine to perform research studies, help care for patients in the Diabetes Control and Complications Trial, attend on the Endocrinology Service, and administrate pharmaceutical research studies. Must be BE/BC in Endocrinology and Metabolism or have extensive experience in diabetes research and patient care. Non-tenured position. Filing deadline is August 15, 1988. Contact Dr David Schade, Department of Medicine, University of NM School of Medicine, 2211 Lomas NE, Albuquerque, NM 87131. AA/EOE.

WOMEN'S HEALTH CENTER in Pleasanton, California seeking a Primary Care Physician. Full-time or part-time. Good salary. Lovely community 40 minutes from San Francisco. Contact Bonnie Rathjen, MD, (415) 463-3442.

FAMILY PRACTITIONERS. BE/BC for pre-paid medical group in San Francisco bay area. Send CV to James Conroy, MD, The Permanente Medical Group, Inc, 260 International Cir, San Jose, CA 95119, or call (408) 972-6339.

INTERNIST needed for multispecialty group of 27 physicians in town of 28,000 in agricultural area 20 miles from state capitol. Clinic adjacent to 150-bed hospital. $60,000 guarantee plus bonus first year. Full stockholder status thereafter plus many fringe benefits. Close to excellent outdoor recreational activities. Contact Mike Crane, 215 E Hawaii, Nampa, ID 83651; (208) 467-1121.

SOUTH DAKOTA, SIOUX FALLS. Expanding physician-owned emergency group has opening for full-time, career-oriented Emergency Physicians in South Dakota. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Send CV to PO Box 805, Cheyenne, WY 82003; or contact Donald Kougl, MD, (307) 632-1436.

WASHINGTON. Expanding physician-owned emergency group has opening for full-time career-oriented Emergency Physicians in south central Washington. Flexible work schedules, excellent working and living conditions. Send CV to EMP, PC, PO Box 805, Cheyenne, WY 82003; or contact Donald Kougl, MD, (307) 632-1436.

URGENT—FP/GP Physicians needed for excellent solo and group opportunities across the US. For information, call (602) 990-8080; or send CV in confidence to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

ORTHOPEDIC SURGEON—BC for Disability Evaluation office. Part- or full-time, regular hours weekdays only, benefits available. Send CV to PO Box 160408, Sacramento, CA 95816.

COTTAGE GROVE, OREGON. Oregon opportunity. Divorced and relocating. Assume $200,000/year Family Practice or be this town's first (and very needed) Pediatrician. Restored fully staffed and equipped office adjacent to grassy park and river. 60-bed hospital with multispecialty coverage. 20 minutes to downtown Eugene, Oregon. Please call Carol King, Business Manager, (503) 942-4413 (daytime).

FAMILY PRACTICE PHYSICIAN needed to work at busy community clinic. In-clinic, on-call (includes OB), and attending responsibilities. Must be Board certified. Locums, full-time, and part-time positions available. If interested, call Sharon Dobie or Linda McVeigh, Country Doctor Community Clinic, (206) 461-4513 or 461-4518.

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Or call (209) 252-3000.

INTERNAL MEDICINE. San Francisco bay area—Immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical house staff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Cir, San Jose, CA 95119.

BC/BE INTERNIST/FAMILY PRACTITIONER needed for growing dynamic general practice. Guaranteed salary with incentive bonuses. Full partnership available after first year. Excellent family and medical environment. Contact Donald L. Rossman, MD, 1055 W Louise Ave, Manteca, CA 95336; (209) 239-4747.

VENTURA (VENTURA COUNTY). Multispecialty group of 35 physicians has immediate positions available for BC/BE Cardiologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Invasive skills preferred. This is an excellent opportunity to join and grow with a successfully expanding group practice in a city chosen by *Money* magazine as one of the ten most preferred cities to live in the USA. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Cardiologist, 2705 Loma Vista Rd, Ventura, CA 93003.

GENERAL SURGEON—RARE OPPORTUNITY, BC/BE, to join internationally recognized Hernia Institute academically oriented. Send CV to Irving Lichtenstein, MD, c/o Lichtenstein Hernia Institute, 9201 Sunset Blvd, Ste 505, Los Angeles, CA 90069.

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VENTURA (VENTURA COUNTY). Multispecialty group of 35 physicians has immediate positions available for BC/BE General Internists. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist, 2705 Loma Vista Rd, Ventura, CA 93003.

SAN DIEGO, CALIFORNIA. Hospital affiliated primary care group seeking additional associates. BC/BE in Family Medicine with minor emergency skills. New state-of-the-art, outpatient primary care centers with excellent compensation package. Send CV to Medical Director, Mercy CarePoint Medical Group, 1011 Camino Del Rio South, #450(4B), San Diego, CA 92108.

FAMILY PRACTICE position available in Berkeley, California. Join two female MDs, two NPs and one PA in a busy, well-established practice. Permanent position to start at mutually agreed upon date in next 18 months. Must do OB. Please write East Bay Family Practice, 2500 Milvia St, Berkeley, CA 94704 or call (415) 540-8200, Edie Silber.

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ONCOLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Gary L. Hillman, Chief, Department of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063.

NORTHERN CALIFORNIA. Opportunity for a full-time position in a hospital-based urgent care center. Compensation is $40-45 per hour and malpractice is paid. If you are BE/BC in a primary specialty, we'd like to talk to you. Send your CV to Northern California Emergency Physicians, PO Box 214584, Sacramento, CA 95821 or call us at (916) 486-4414.

INTERNIST, BC/BE, California license. Duties will include outpatient, admissions, and in-patient care. Send résumé to Dr Susan J. Steinberg, Medical Director, Access Health Care, 26 California St, San Francisco, CA 94111.

BC/BE CARDIOLOGIST to join three invasive/noninvasive Cardiologists in practice, Portland, Oregon metropolitan area. Send CV to Number 105, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

INDUSTRIAL PHYSICIAN, California central coast. Successful Internal Medicine clinic with immediate opening for full-time MD. No nights or weekends. Internal Medicine experience desirable, Family Practice or Emergency Medicine background acceptable. Paid malpractice. Income competitive based on experience. Growing community of 80,000. Send CV to R. D. Shaw, MD, 1400 E Church St, Santa Maria, CA 93454; (805) 922-5811, ext 196.

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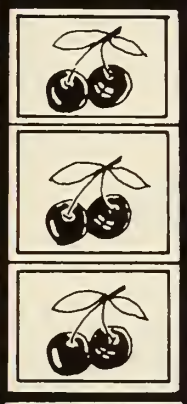

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RURAL COLORADO. Eight physician group practice is seeking BC/BE Family Practitioner, Med/Peds, or Internal Medicine Physician with an interest in some Pediatric care. Competitive salary, excellent recreational opportunities in a high mountain, agricultural valley. Contact Kris Steinberg, MD, (719) 589-2562; 1710 First St, Alamosa, CO 81101.

INTERNAL MEDICINE/CARDIOLOGY BC/BE to join busy multispecialty six doctor group located in medically sophisticated small community. Easy access to Seattle, Vancouver, BC, and San Juan Islands. Send CV to Harold R. Clure, MD, Fidalgo Medical Associates, PS, 24th & M Ave, Anacortes, WA 98221; or call (206) 293-3101.

OCCUPATIONAL/FAMILY PRACTICE. Excellent opportunities with the West Coast's leading provider of Occupational/Family Practice medicine. Full/part-time positions throughout California and Washington (Seattle/Tacoma). Current license/CPR. Prior out-patient/family practice/industrial-type trauma experience. Attractive package includes guaranteed salary, incentives, benefits, malpractice; we offer trained staff, experienced marketing and a network of diverse medical services. Contact Personnel Director, ReadiCare, Inc, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (800) 237-3234, (408) 737-8531. Join our dynamic team of professionals. Practice and live in an incomparable environment.

ORTHOPEDIST. The West Coast's leading Occupational/Family Practice medical provider has full-time/part-time opportunities for Orthopedic Specialists in California and Washington (Seattle/Tacoma). Attractive package includes guaranteed salary, incentive bonus and benefits. Current license. Contact Thom Catlett, Vice President, 3 Corporate Plaza, #206, Newport Beach, CA 92660; call COLLECT (714) 476-8743. Join our dynamic team of professionals. Practice and live in an incomparable environment.

FEMALE ORIENTED PRACTICE. Great potential for Family Practitioner or Internist with emphasis on primary care of women (no OB) in a small college town, Rocky Mountain setting. Associate, join or coverage with solo Internist. Must be easy to work with and have good patient rapport. Reply to Number 104, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ENDOCRINOLOGIST BC/BE, with interest in diabetes, to assume established practice. Join a dynamic group of 10 Internists/Specialists. Outstanding initial guarantees and financial incentives. City of 50,000 is a regional referral center for 250,000. Local recreational and educational opportunities abound in this Pacific Northwest city with sunbelt climate. Send CV to Chris Nauta, Administrator, Internal Medicine Associates of Yakima, Inc, PS, 316 Holton Ave, Yakima, WA 98902.

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(Continued on Page 130)

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INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, PO Box 7602, San Francisco, California 94120-7602. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar, and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables, and references) on one side of the paper, with 1½-inch margins. Articles should not exceed 3,000 words (less than 15 text pages typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page. Manuscripts produced with a dot-matrix printer are ordinarily not acceptable.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. Use Système International (SI) units throughout the manuscript. Provide metric equivalents for all SI units; they will be noted parenthetically in the published text.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name, including salt or ester, should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses, and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented," or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title, and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and the position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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References

References should be limited to those cited in the text and should be to medical, scientific, or scholarly publications. (Mass circulation periodicals are referenced in parentheses in the text.) They must be typed double-spaced and numbered consecutively as they appear in the manuscript.* (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, use of inclusive page numbers, and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs, or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was oral or written, and the person's name, highest academic degree, and professional affiliation should be provided.

**Exception:* Articles for Topics in Primary Care and Epitomes use a limited number of authoritative references, both to the specific topic and the subject as a whole, that are *not* cited in the text and are listed in alphabetic order.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians, or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects, and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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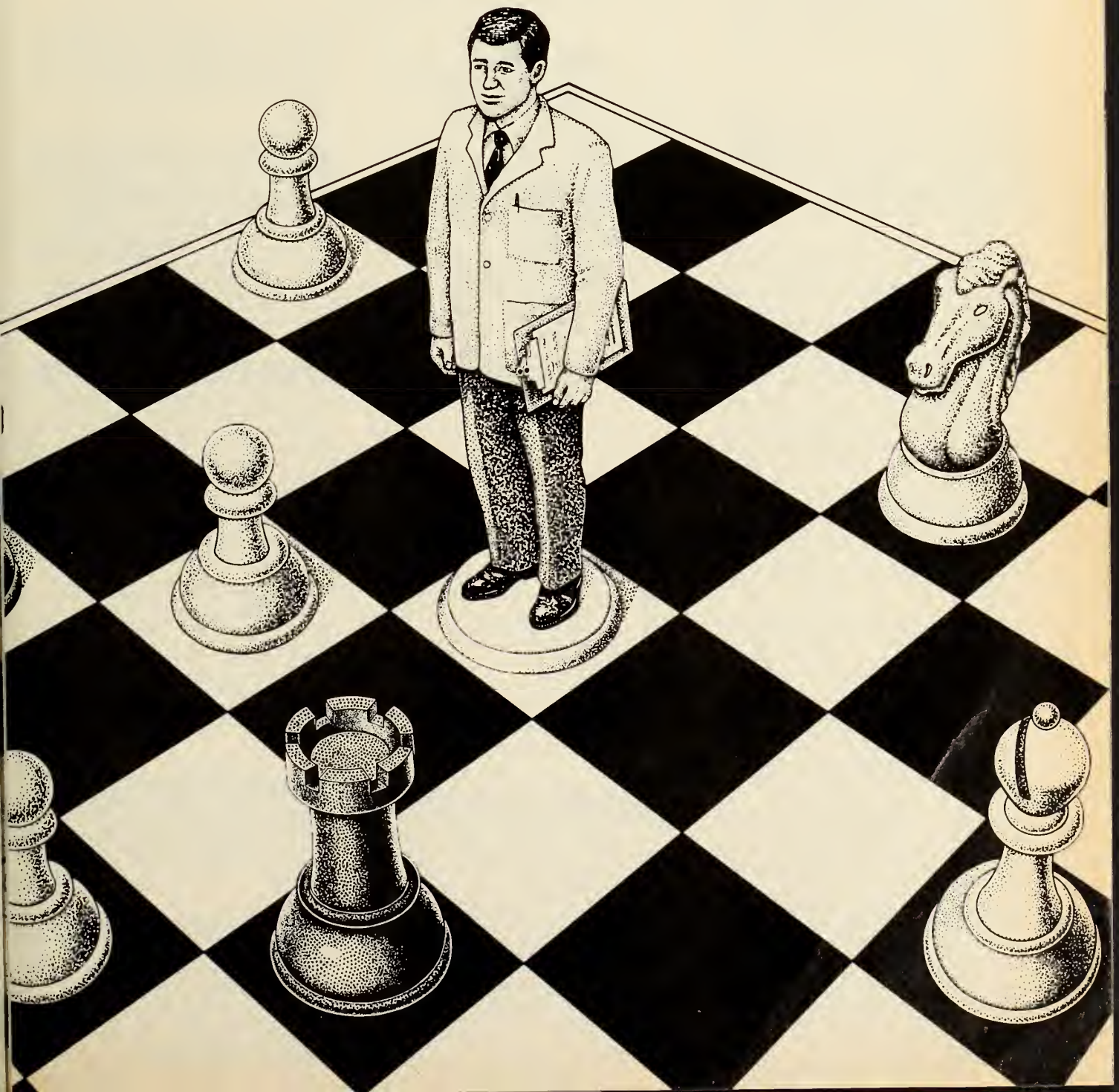

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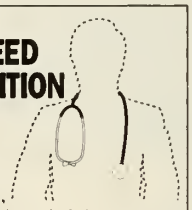

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INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*)

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

SURGICAL PROPHYLAXIS Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e g , vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (e g , during coronary artery bypass surgery)

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

Rarely, shadows suggesting sludge have been detected by sonograms of the gallbladder in asymptomatic and symptomatic patients This appears to be reversible on discontinuation of therapy In a few symptomatic patients receiving higher than usual doses, who underwent surgery, sludge containing traces of ceftriaxone was recovered from surgical specimens Discontinue therapy in patients who develop signs or symptoms suggestive of gallbladder disease, consider conservative management

PRECAUTIONS: *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g , chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum

ROCEPHIN® (ceftriaxone sodium/Roche)

duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose

There are however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin Exercise caution before administration to hyperbilirubinemic neonates, especially prematures

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I V administration

HYPERSENSITIVITY—rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL—diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC—elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL—elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria hematuria anaphylaxis, bronchospasm serum sickness, abdominal pain colitis flatulence dyspepsia palpitations and epistaxis

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone, piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone, bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION)

Also supplied as a sterile crystalline powder as follows

ADD-Vantage Vials** containing 1 gm or 2 gm equivalent of ceftriaxone

Also supplied premixed as a frozen iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose plastic containers,† as follows

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1 9 gm dextrose hydrous, USP added

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1 2 gm dextrose hydrous, USP added

NOTE Rocephin in the frozen state should not be stored above -20°C

*Registered trademark of Abbott Laboratories, Inc

†Manufactured for Roche Laboratories, Division of Hoffmann-La Roche Inc , by Travenol Laboratories, Inc , Deerfield, Illinois 60015

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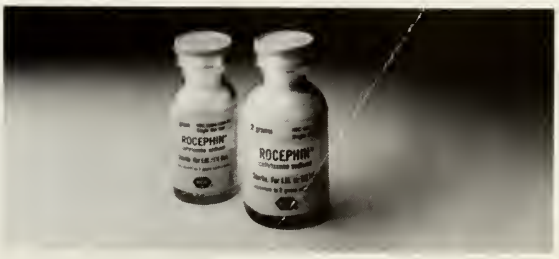

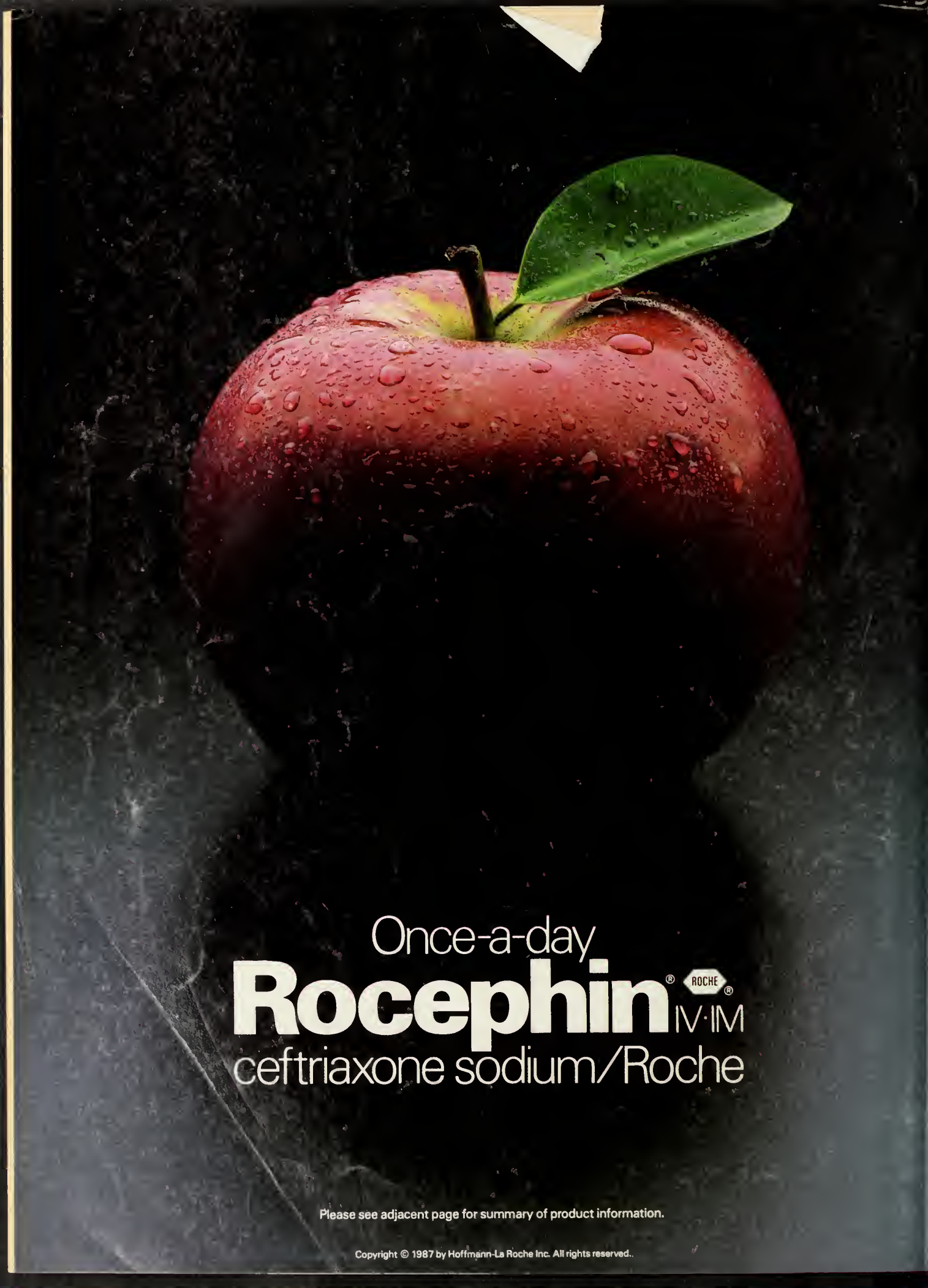
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Well-controlled clinical trials confirm:

ZANTAC 150 mg hs significantly superior to cimetidine 400 mg hs for maintenance therapy in healed duodenal ulcers.

FREE FUTURE

Percent of patients ulcer-free after 1 year of therapy

ZANTAC 150 mg hs (n = 60)	84%*
cimetidine 400 mg hs (n = 66)	57%
ZANTAC 150 mg hs (n = 243)	77%†
cimetidine 400 mg hs (n = 241)	63%

*P = 0.01 †P = 0.0004 % life-table estimates

All patients were permitted prn antacids for relief of pain.
Adapted from Silvis[1] and Gough.[2]

These two trials[1,2] used the currently recommended dosing regimen of cimetidine (400 mg hs) and ranitidine (150 mg hs). A comparison of other dosing regimens has not been studied.
The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid.
The superiority of ranitidine over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets hs

Glaxo/ ROCHE

See next page for references and Brief Summary of Product Information.

References: 1 Silvis SE Griffin J Hardin R, et al Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer *J Clin Gastroenterol* 1985,7(6) 482-487 2 Gough KR, Korman MG Bardhan KD, et al Ranitidine and cimetidine in prevention of duodenal ulcer relapse A double-blind randomised multicentre, comparative trial *Lancet* 1984 2 659-662

ZANTAC® 150 Tablets
(ranitidine hydrochloride)

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only Before prescribing, see complete prescribing information in ZANTAC® product labeling

INDICATIONS AND USAGE: ZANTAC® is indicated in
1 Short-term treatment of **active duodenal ulcer**. Most patients heal within four weeks
2 **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers
3 The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis)
4 Short-term treatment of **active, benign gastric ulcer**. Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated
5 Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within one or two weeks after starting therapy Therapy for longer than six weeks has not been studied

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug

PRECAUTIONS: General: 1 Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy
2 Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION) Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution)

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks

Pregnancy: ***Teratogenic Effects. Pregnancy Category B***: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: ZANTAC is secreted in human milk Caution should be exercised when ZANTAC is administered to a nursing mother

Pediatric Use: Safety and effectiveness in children have not been established

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC® The relationship to ZANTAC therapy has been unclear in many cases Headache, sometimes severe, seems to be related to ZANTAC administration

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort pain

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice

Musculoskeletal: Rare reports of arthralgias

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia

Other: Rare cases of hypersensitivity reactions (eg bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated Doses up to 6 g/day have been employed in patients with severe disease

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day

GERD: The current recommended adult oral dosage is 150 mg twice a day

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47)

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

May 1988

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Patients in North America with biopsy-proven myocarditis may now be enrolled in an NIH-funded, placebo-controlled, randomized trial evaluating efficacy of cyclosporine. Referral of the patient is not necessary. Cyclosporine and a small grant are provided.

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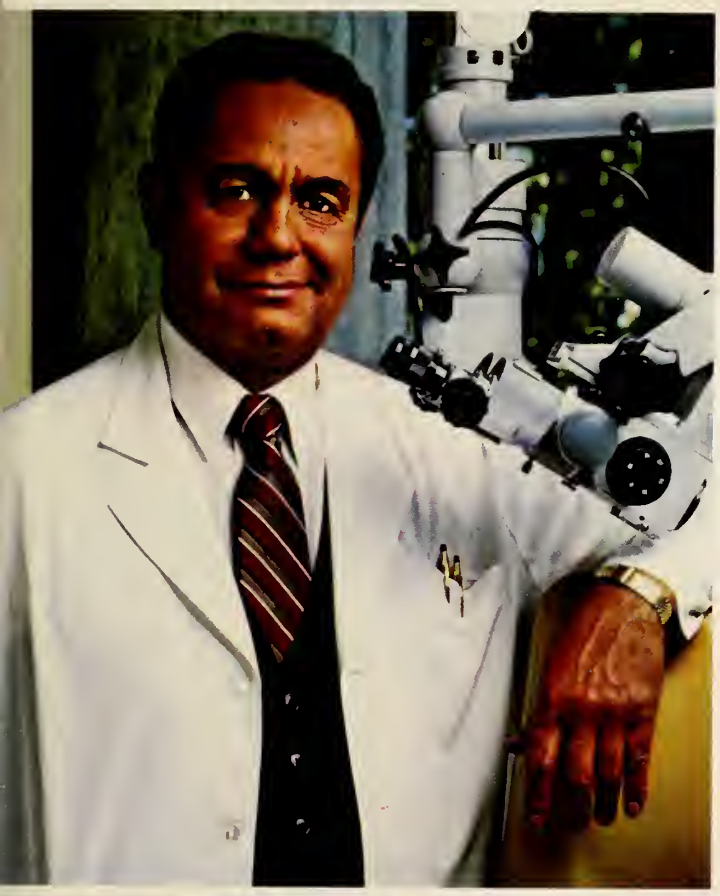

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OUTSTANDING ACHIEVEMENTS Freshman Medical Student Research Award; Class President – 2nd year medical school; Student Body President – senior year medical school; Special Award by National Institute of Health to attend and present paper at International Congress of Otolaryngology in Tokyo, Japan; Chairman, Department of Otolaryngology, San Francisco General Hospital 1970-76; Chief of Medical Staff, Franklin Hospital 1982-84.

Dr. Tipton and residents examining post-operative patient in recovery room.

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Brief Summary. Consult the package insert for prescribing information.

Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg h s after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions—No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b i d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement compared to concurrent controls, and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay.

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating rats. Pups reared by treated lactating rats had depressed growth rates. Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported, it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported.

Overdosage: There is little clinical experience with overdosage of Axid in humans. If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous LD_{50} values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively. PV 2091 AMP [041288]

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Lilly

Eli Lilly and Company
Indianapolis, Indiana
46285

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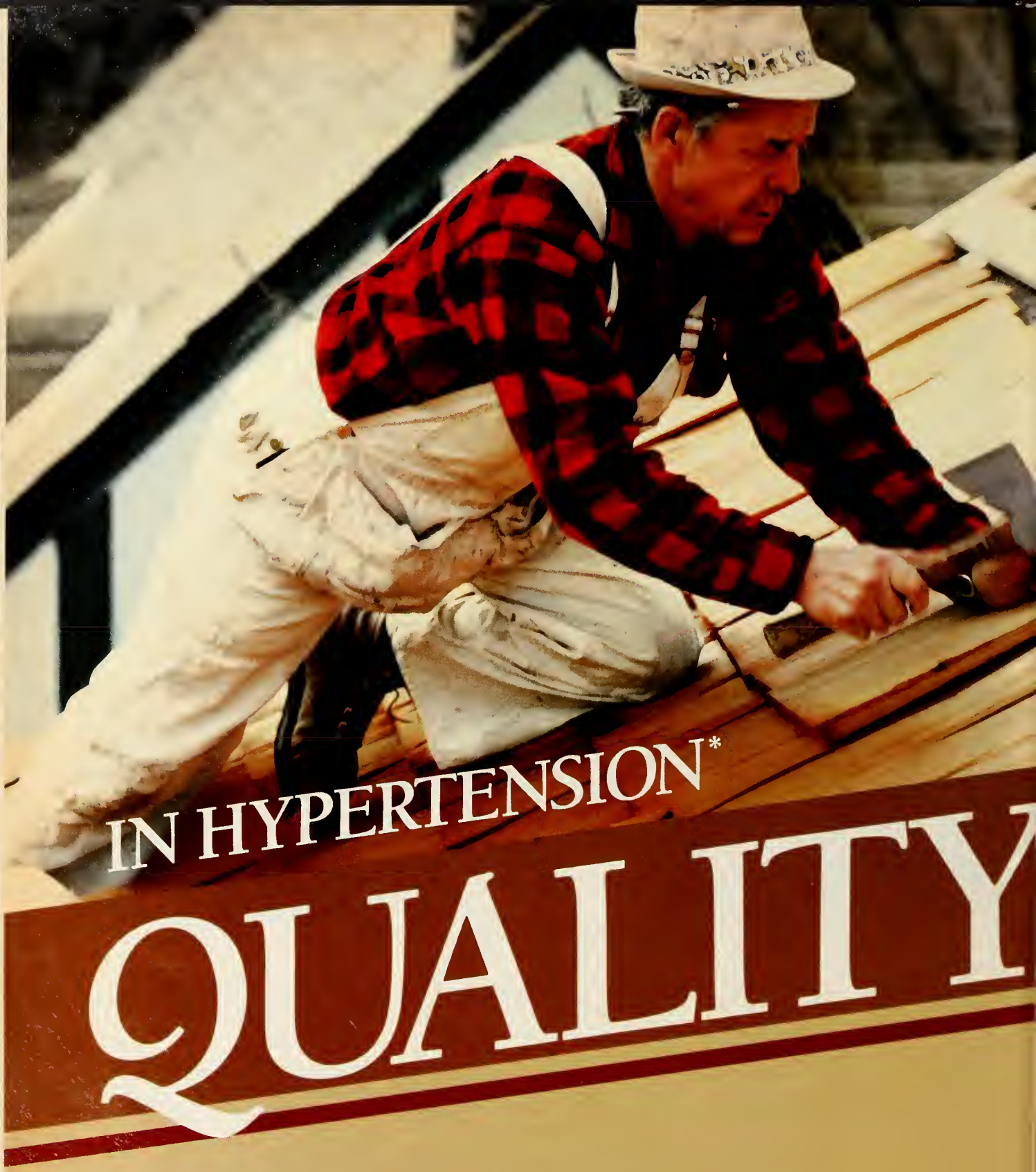

*CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.

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Means a job well done.

We spend so much of our lives at work...it's no wonder our work performance is key to our quality of life. Work performance is also a key factor in assessing antihypertensive therapy. CAPOTEN improved hypertensive patients' work performance (e.g., ability to keep pace with the job, concentration, job satisfaction, less on-the-job fatigue).[1] So, for hypertensive patients who work, why not prescribe the antihypertensive that can work for them... CAPOTEN.

These data are based on a multicenter, randomized, 24-week study of 626 mild-to-moderate hypertensive male patients with normal renal function, 181 of whom received captopril.

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CAPOTEN® TABLETS

Captopril Tablets

INDICATIONS: Hypertension – CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis – Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥ 1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function* – Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia* – If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension – Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity – In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis – Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal – About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic – Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic – Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients – reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular – Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia – Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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★ Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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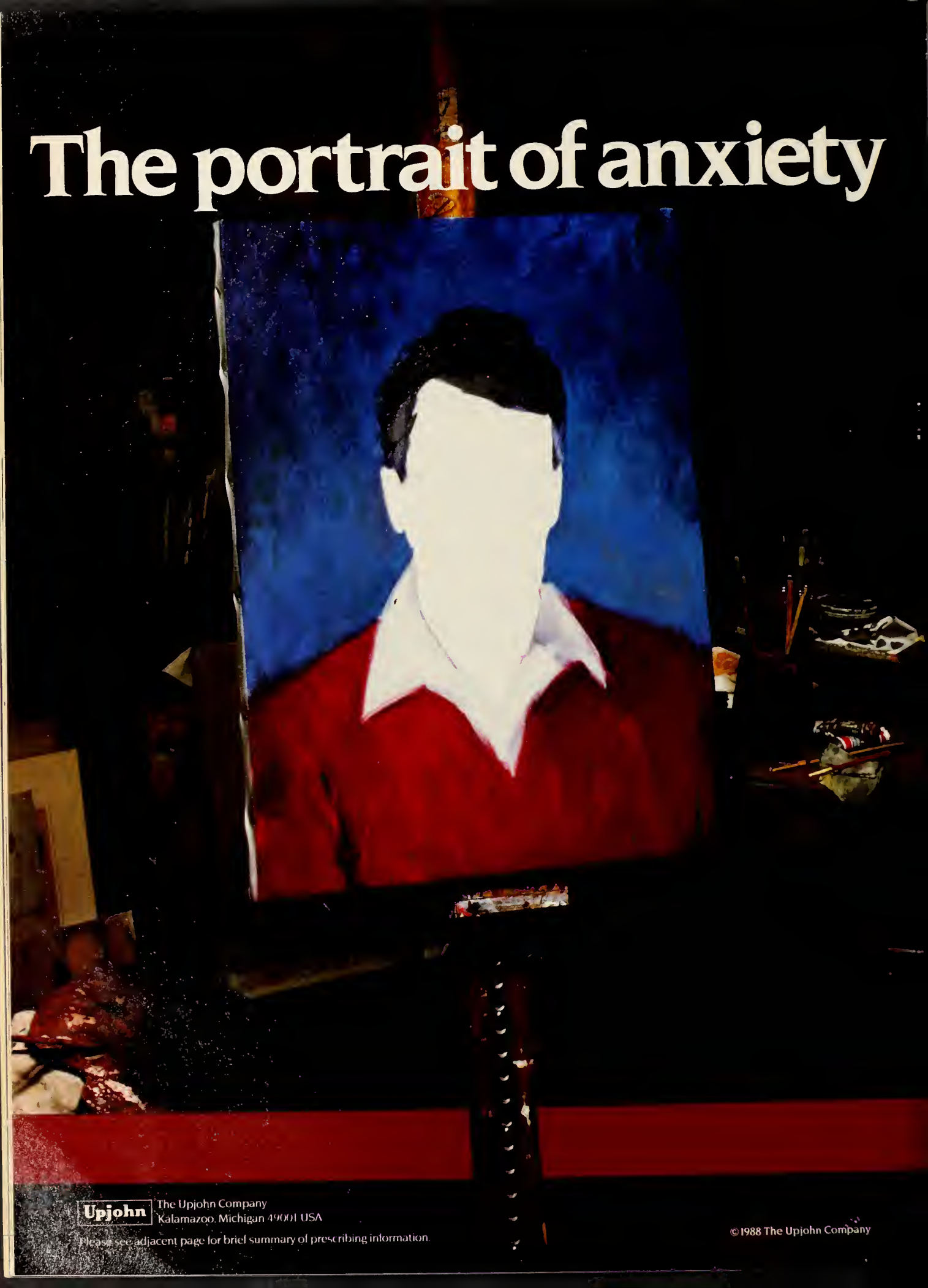
The portrait of anxiety



Upjohn The Upjohn Company
Kalamazoo, Michigan 49001 USA

Please see adjacent page for brief summary of prescribing information.

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is often complicated

With associated depressive symptoms.

In double-blind, four-week clinical trials in 632 patients with moderate to severe anxiety, therapy with XANAX was compared with placebo.

XANAX was significantly more effective ($P<.001$) than placebo in relieving the anxiety, with over half of the patients showing marked to moderate improvement by the first evaluation period (one week).

In addition, over 70% of these patients experienced associated moderate to severe depressed mood. XANAX was shown to be significantly more effective ($P<.014$) than placebo in improving the associated depressed mood.

With associated cardiovascular symptoms.

Almost 60% of patients in the study had anxiety with associated cardiovascular symptoms even though cardiovascular disease had been ruled out. XANAX was shown to effectively relieve anxiety including the associated cardiovascular symptoms.

XANAX, the first of a unique class—the triazolobenzodiazepines.

- *Well tolerated*—Side effects, if they occur, are generally observed at the beginning of therapy and usually disappear with continued medication. Drowsiness and light-headedness were the most commonly reported adverse reactions.
- *Sustained efficacy*—No reported increase in dosage during 16-week clinical study, once an appropriate dosage was achieved. Since long-term effectiveness of XANAX has not been established, it is recommended that it not be used for longer than 16 weeks.
- *Simple dosage*—0.25 to 0.5 mg t.i.d.

TABLETS 0.25, 0.5 & 1 MG

Xanax®

alprazolam IV

for the relief of complicated anxiety

XANAX® Tablets
(alprazolam) ©

INDICATIONS AND USAGE
Anxiety disorders, short-term relief of the symptoms of anxiety, and anxiety associated with depression. Anxiety or tension associated with the stress of everyday life usually does not require an anxiolytic. Effectiveness for more than four months has not been established; periodically reassess the usefulness of the drug for the individual patient.

CONTRAINDICATIONS
Sensitivity to XANAX or other benzodiazepines, and in acute narrow angle glaucoma

WARNINGS
Benzodiazepines can cause fetal harm in pregnant women, hence women who may become pregnant should be warned. Avoid during the first trimester. Withdrawal seizures have been reported upon rapid dose reduction or abrupt discontinuation, thus reduce dose gradually. (See Drug Abuse and Dependence and Dosage and Administration.)

PRECAUTIONS
General: If XANAX is combined with other psychotropics or anticonvulsants, consider drug potentiation. (See Drug Interactions). Use the usual precautions in patients with renal or hepatic impairment and regarding prescription size in depressed and suicidal patients. In elderly and debilitated patients, use the lowest possible dose. (See Dosage and Administration.) Hypomania and mania has been reported in depressed patients.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests*: Not ordinarily required in otherwise healthy patients. *Drug Interactions*: Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Plasma levels of imipramine and desipramine are increased. Pharmacokinetic interactions with other drugs have been reported. Cimetidine can delay clearance of benzodiazepines. *Drug/Laboratory Test Interactions*: No consistent pattern for a drug or test. *Carcinogenesis, Mutagenesis, Impairment of Fertility*: No carcinogenic potential or impairment of fertility in rats. *Pregnancy*: See Warnings. *Nonteratogenic Effects*: The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms, neonatal flaccidity and respiratory problems. *Labor and Delivery*: No established use. *Nursing Mothers*: Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use*: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness. *Gastrointestinal*: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation. *Cardiovascular*: Tachycardia/palpitations, and hypotension. *Sensory*: Blurred vision. *Musculoskeletal*: Rigidity and tremor. *Cutaneous*: Dermatitis/allergy. *Other side effects*: Nasal congestion, weight gain, and weight loss.

Withdrawal seizures with rapid decrease or abrupt discontinuation. (See Warnings.)

The following adverse events have been reported with benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, seizures, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence, and urinary retention.

Paradoxical reactions such as stimulation, agitation, rage, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

Liver enzyme elevations, gynecomastia and galactorrhea have been reported but no causal relationship was established.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms including seizures have occurred following abrupt discontinuance or rapid dose reduction of benzodiazepines. (See Warnings). Dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class*: XANAX is a controlled substance and has been assigned to schedule IV.

OVERDOSAGE
Manifestations include somnolence, confusion, impaired coordination, diminished reflexes and coma. No delayed reactions have been reported.

DOSAGE AND ADMINISTRATION
Dosage should be individualized.

The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than 0.5 mg every three days.

HOW SUPPLIED
XANAX Tablets are available as 0.25 mg, 0.5 mg, and 1 mg tablets.

CAUTION:
FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-7-S

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2nd Annual
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San Francisco

Conference is designed to help local health departments, community leaders, and funders organize a comprehensive community-wide response to the AIDS epidemic.

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Community-based, non-profit agency official staff: $50
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Conference registration contact:
1988 National AIDS Conference
c/o Krebs Convention Management Services
555 De Haro, Suite 200
San Francisco, CA 94107
Phone: (415) 255-1297

THE INSIDE STORY
IN HYPERTENSION

PEEL

PEEL

PEEL

TRANDATE® *bid*

labetalol HCl/Glaxo 100 mg tablets

Because it vasodilates

THE OUTSIDE STORY

UNCOMPROMISED VITALITY

- ☐ Low incidence of fatigue and impotence[7]
- ☐ Preserves exercise tolerance[5]
- ☐ High level of patient acceptance

Trandate Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

For references and a complete listing of reported adverse reactions, including incidence at various dosage levels, please see ADVERSE REACTIONS section of the Brief Summary of Prescribing Information on next page.

Please see next page for references and Brief Summary of Prescribing Information.

Effective blood pressure control

TRANDATE®bid

labetalol HCl/Glaxo 100 mg tablets

Because it vasodilates

References: 1. Malini PL, Strocchi E, Negroni S, et al: Renal haemodynamics after chronic treatment with labetalol and propranolol. *Br J Clin Pharmacol* 1982;13(suppl 1):123S-126S **2.** Pedersen EB, Larsen JS: Effect of propranolol and labetalol on renal haemodynamics at rest and during exercise in essential hypertension. *Postgrad Med J* 1980;56(suppl 2):27-32. **3.** Wallin JD: Antihypertensives and their impact on renal function. *Am J Med* 1983;75:103-108. **4.** Koch G: Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol. *Br Heart J* 1979;41(2):192-198. **5.** Feit A, Holtzman R, Cohen M, et al: Effect of labetalol on exercise tolerance and double product in mild to moderate essential hypertension. *Am J Med* 1985;78:937-941. **6.** Lund-Johansen P: Short- and long-term (six-year) hemodynamic effects of labetalol in essential hypertension. *Am J Med* 1983;75:24-31. **7.** Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:285-293.

TRANOATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphysema): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy before major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see PRECAUTIONS: Drug Interactions).

PRECAUTIONS: General: *Impaired Hepatic Function:* TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will

TRANOATE® Tablets (labetalol hydrochloride)

be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multicenter, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, headache. ***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, taste distortion. ***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, drowsiness. ***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, increased sweating. ***Cardiovascular:*** Edema, postural hypotension. ***Respiratory:*** Dyspnea. ***Skin:*** Rash. ***Special Senses:*** Vision abnormality, vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including, rarely, syncope. ***Central and Peripheral Nervous Systems:*** Paresthesia, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment. ***Collagen Disorders:*** Systemic lupus erythematosus; positive antinuclear factor (ANF). ***Eyes:*** Dry eyes. ***Immunological System:*** Antimitochondrial antibodies. ***Liver and Biliary System:*** Cholestasis with or without jaundice. ***Musculoskeletal System:*** Muscle cramps, toxic myopathy. ***Respiratory System:*** Bronchospasm. ***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia. ***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents: ***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on psychometrics. ***Cardiovascular:*** Intensification of AV block (see CONTRAINDICATIONS). ***Allergic:*** Fever combined with aching and sore throat, laryngospasm, respiratory distress. ***Hematologic:*** Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. ***Gastrointestinal:*** Mesenteric artery thrombosis, ischemic colitis. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

April 1988

Glaxo

Glaxo Inc., Research Triangle Park, NC 27709

Continuing Medical Education

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 21-23—**Diagnosis and Management of Respiratory Diseases.** The Boulders, Scottsdale. Fri-Sun. Contact: Medical Education Resources, 1 (800) 421-3756.

November 11-13—**17th Annual Seminar—Musculoskeletal Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Department of Radiology, Maricopa Medical Center, (602) 267-5361.

December 3-4—**Annual Meeting of the Arizona Chapter of the American College of Surgeons.** Rancho de los Caballeros, Wickenburg. Sat-Sun. Contact: Lee Ansel, MD, Program Chairman, (602) 251-3131.

March 4-8—**Third Annual Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, Barrow Neurological Institute, (602) 285-3956.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

October 14—**18th Course on Allergy and Immunology.** Pacific Presbyterian Medical Center at San Francisco. Fri. Contact: Herbert S. Kaufman, MD, PPMC, 2340 Clay St, Rm 313, San Francisco 94115. (415) 923-3441.

ANESTHESIOLOGY

August 21-27—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Inter-Continental Hotel, Wailea, Maui. Sun-Sat. 20 hrs. $325/$375. Contact: CSA, 1065 E. Hilldale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 10-11—**Case Conference in Anesthesia.** California Society of Anesthesiologists at High Sierra Hotel, Lake Tahoe. Sat-Sun. 9 hrs. $160. Contact: CSA, 1056 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

September 30-October 1—**Anesthesia Practice 1988.** Anesthesiology Educational Foundation. Fri-Sun. 11 hrs. Contact: AEF, PO Box 24230, Federal Building, Los Angeles 90024. (213) 825-0736.

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologist at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 29-February 3—**Clinical Update in Anesthesiology.** Tucson Hospitals Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray G. Atnikov, MD, c/o Box F110-63, Blaine, WA 98230. (604) 874-5291.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 156)

The Eleventh Annual

Heart Symposium

Presented by
Southern California Heart Center of Northridge Hospital Medical Center
Saturday, October 1, 1988, 8 a.m. to 5 p.m. at Century Plaza Hotel, Los Angeles

Forrester Holmes Illingworth Johnson Shell
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"Treatment of Coronary Artery Disease — The 21st Century"
"Coronary Angioplasty in Acute Myocardial Infarction and Complex Disease"
"The Lipid-Coronary Connection: Diagnosis and Management"
"New Frontiers in Coronary Artery Surgery"
"Ventricular Arrhythmias: Electrophysiologic Studies, Drugs and Surgical Therapies"
"Silent Ischemia: Classification, Management and Treatment"
"Heart-Lung Transplantation"
"Controversies in Cardiology: Does Treatment Really Work?"
"Pathology of Coronary Thrombolysis, Coronary Angioplasty and Balloon Valvuloplasty"

James S. Forrester, M.D.
David Holmes, Jr., M.D.
D. Roger Illingworth, M.D., Ph.D.
W. Dudley Johnson, M.D.
Melvin M. Scheinman, M.D.
William E. Shell, M.D.
Julie A. Shinn, R.N., M.A.
David H. Spodick, M.D., D.Sc.
Bruce Waller, M.D.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 152)

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sat-Sun. Contact: Murray G. Atnikov, MD. (604) 874-5291.

CARDIOLOGY

August 25-26—**Advanced Fetal Heart Rate Monitoring.** Center for Health Education at Red Lion Resort, Santa Barbara. Thurs-Fri. Contact: The Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801.

October 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hyatt on Union Square, San Francisco. Fri-Sat. $295. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

August 21-28—**International Symposium: Hot Spots in Dermatology.** Kauai Medical Group at Molokai, Hawaii. One week. Contact: David Elpern, MD, 3420-B Kuhio Highway, Lihue, Hawaii 96766. (808) 245-1507.

EMERGENCY MEDICINE

August 22-26—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II & Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

August 29-September 2—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Mon-Fri. 31 hrs. $420. Contact: UCSF.

October 10-14—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium I & Optional Advanced Emergency Procedures Laboratory.** UCSD at Catamaran Resort Hotel, San Diego. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 21-23—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

November 4-6—**Management of the Child With Head Injury.** Children's Hospital Oakland at Monterey Conference Center and Hotel Pacific, Monterey. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, Continuing Medical Education, Children's Hospital Oakland, 747-52nd St, Oakland 94609. (415) 428-3021.

November 7-10—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Imperial Palace, Las Vegas, Nevada. Mon-Thurs. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

November 14-18—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III & Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 4-9—**Current Concepts in Emergency Care.** Institute for Emergency Medical Education at Royal Lahaina Resort, Maui, Hawaii. Sun-Fri. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. (800) 524-5264.

December 5-9—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II & Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

January 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. $450. Contact: UCSD.

January 26-30—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Maui Marriott, Maui, Hawaii. Thurs-Mon. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

January 27-29—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

February 19-24—**Emergency Medicine.** UCD. Sun-Fri. Contact: UCD.

INTERNAL MEDICINE

August 21-26—**New Advances in Internal Medicine: Clinical Applications.** UCD at Hyatt Regency, Monterey. Sun-Fri. 23 hrs. $410. Contact: UCD.

August 28-31—**Under Pressure II: Glaucoma 1988.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Wed. 12 hrs. $335. Contact: UCD.

September 8-10—**New Advances in Common Neurologic Disorders.** UCSD Division of Neurology at Catamaran Resort Hotel, San Diego. Thurs-Sat. 14 hrs. $300. Contact: Shirley Kolkey, Conference Coordinator, 3770 Tansy, San Diego 92121. (619) 453-6222.

September 15-18—**Medical Acupuncture for Physicians: Part I.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. Thurs-Sun. 200 hrs. $3,200. Contact: UCLA.

September 22-24—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. Contact: Dr Luis M. de la Maza, Department of Pathology, Rt 84, UCI Medical Center, 101 City Drive S., Orange, 92668. (714) 634-6868.

October 4-7—**Rheumatology and Clinical Immunology.** UCSF at Stanford Court, San Francisco. Tues-Fri. 19 hrs. $395. Contact: UCLA.

October 14-15—**13th Annual Clinical Neurosciences Symposium.** Dominican Neurologic Institute at Chaminade Conference Center, Santa Cruz. Fri-Sat. 11 hrs. $350. Contact: Karen Rickenbach, Dominican Hospital, 1555 Soquel Dr, Santa Cruz 95065. (408) 462-7562.

November 3-5—**New Directions in Anti-viral Chemotherapy.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. $100. Contact: UCSF.

November 7-9—**12th Annual Cancer Symposium.** Scripps Memorial Cancer Hospital at Sheraton Harbor Island Hotel E, San Diego. Mon-Wed. 21 hrs. $390. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

November 11-14—**The Spine: Current Concepts of Diagnosis and Treatment.** The Spine Study Group at Marriott Desert Springs Resort, Palm Springs. Fri-Mon. $250. Contact: The Spine Study Group, PO Box 33185, San Diego 92103. (619) 692-9115.

November 16—**Common Musculoskeletal Problems.** VA Medical Center Sepulveda. 6 hrs. Contact: Arun J. Mehta, Rehabilitation Medicine Service (117), VA Medical Center, Sepulveda 91343. (818) 891-2473.

December 1-2—**Recent Advances in Occupational Cancer.** UCSF at Hotel Meridien, San Francisco. Thurs-Fri. $220. Contact: UCSF.

December 30-January 8—**Medical Acupuncture for Physicians: Part II.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. 10 days. 200 hrs. $3,200. Contact: UCLA.

January 6-7—**6th Annual Reider Laser Symposium—Urology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 25-27—**12th Annual: Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wed-Fri. 21 hrs. $400. Contact: Edith S. Bookstein, NNN, PO Box 2586, La Jolla 92038. (619) 454-3212.

OB/GYN

August 19-21—**1988—Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates and San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

November 10-13—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sat. Contact: UCI.

November 12—**Infertility Update V.** Scripps Clinic and Research Foundation Amphitheater, La Jolla. Sat. 7 hrs. $110. Contact: Bonny Mower, Box 400S, Dept of Academic Affairs, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

November 13-19—**11th Annual Review Course in Clinical Obstetrics & Gynecology.** The Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach, 90801-1428. (213) 595-3811.

January 6-7—**6th Annual Reider Laser Symposium—Gynecology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 156)

January 29-February 2—**Ob/Gyn.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

ORTHOPEDICS

October 21-23—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, Medical Education, PO Box 84296, San Diego 92138. (619) 223-2997.

January 21-28—**Orthopaedic Emergencies.** Scripps Memorial Hospital Encinitas at Kona Surf Resort, Kona, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 12—**1989 Interim Meeting of American Orthopaedic Society of Sports Medicine.** American Orthopaedics Society for Sports Medicine at Las Vegas, Nevada. Sun. Contact: AOSSM, 70 W Hubbard St, Ste 202, Chicago, IL 60610. (312) 644-2623.

PEDIATRICS

August 22-24—**Pediatrics Update: 1988.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 18 hrs. $295. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

September 24-25—**45th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Los Angeles Hilton Hotel. Sat-Sun. $175. Contact: Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305.

October 13-16—**Advanced Fetal Heart Rate Monitoring.** Center for Health Education at Embassy Suites, Napa. Thurs-Sun. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

October 15-20—**American Academy of Pediatrics Annual Session.** AAP. Sat-Thurs. Contact: AAP, 1801 Hinman Ave., Evanston, IL 60201.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

November 4-6—**Current Advances in Pediatrics.** Orange County Psychiatric Society at Disneyland Hotel, Anaheim. Fri-Sun. 14 hrs. Contact: OCPS California Chapter 4, PO Box 1297, Orange 92668. (714) 978-2415.

December 3—**7th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Educational Center, San Diego. Sat. 7 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 27-29—**27th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott. Fri-Sun. 15 hrs. $225. Contact: Katherine Barky, MD, Childrens Hospital, PO Box 54700, Los Angeles 90054.

February 10-12—**Current Concepts in Pediatric Medicine.** Children's Hospital & Health Center at Marriott Hotel, San Diego. Wed-Fri. Contact: Children's Hospital & Health Center, Continuing Medical Education Office, 8001 Frost St, San Diego 92123. (619) 576-4072.

PSYCHIATRY

August 24-29—**The Neuropsychiatric Aspects of Politics and Politicians.** Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, Hawaii. Wed-Mon. 24 hrs. Contact: Barbara Harwell, SCNPI, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

November 18-20—**34th Annual Group Therapy Symposium.** UCSF. Fri-Sun. Contact: UCSF.

January 22-27—**15th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. Contact: UCD.

RADIOLOGY

August 22-26—**Radiology: 1988 USC Radiology Summer Hawaiian Seminar.** USC at Kauai Westin, Lihue, Hawaii. Mon-Fri. 28 hrs. $475. Contact: USC.

August 25-28—**Fourth Annual Physics and Biology of Radiology.** UCSD at La Jolla Village Inn. Thurs-Sat. 25 hrs. $395. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

(Continued on Page 160)

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House of Delegates Opening Session Highlights

KEYNOTE SPEAKER

Daniel Callahan, PhD, will be the keynote speaker at Thursday's House of Delegates opening session.

Daniel Callahan, PhD

Dr. Callahan is the author of "Setting Limits: Medical Goals in an Aging Society," a book that proposes federal expenditures for certain procedures be limited to people under 70 years of age.

Dr. Callahan is co-founder and director of the Hastings Center, Briarcliff Manor, New York, a research and educational organization founded in 1969 to examine ethical issues in medicine, biology and the professions.

He is an elected member of the Institute of Medicine, National Academy of Sciences, a former member of the Task Force on Life and Law of New York State, and a fellow of the American Association for the Advancement of Science.

Special Appearance:

Governor Gardner To Address House

WAMPAC Supports Booth

Governor Booth Gardner will round out the Opening Session when he speaks to the House of Delegates at 4:30 p.m. on Thursday.

Governor Booth Gardner

WAMPAC is sponsoring the Governor's talk, followed by a WAMPAC fundraiser. Look for location and time details of the moneyraiser at the registration desk.

The WAMPAC fundraiser is your chance to personally show the Governor your appreciation of his efforts on behalf of organized medicine, particularly his signing of the Liability Reform Act of 1986 with no changes.

WAMPAC fully supports the Governor's re-election and encourages physicians to participate in his campaign.

A special thank you to Laurie Barron, MD, of Yakima, chairman of this year's Annual Meeting scientific program.

THE REACTOR PANEL

Because of the controversial nature of Dr. Callahan's proposals, a three-member reactor panel will offer opinions and alternatives to "Setting Limits."

Johnny Cox, RN, PhD, staff ethicist at Sacred Heart Medical Center in Spokane, is one of only a few persons working fulltime as a clinical ethicist in the U.S. outside of a university medical center.

Johnny Cox, RN, PhD

A former director of the Health and Human Values program at Seattle's Providence Medical Center, Dr. Cox is co-founder of the Hopsice of Spokane, the first hospice to provide clinical care in the Pacific Northwest.

He is a familiar face to many WSMA physicians because of his long-standing involvement with medical-ethical concerns, including Natural Death Act revisions and the issue of living wills.

Eva N. Skinner, RN, of Los Angeles is a board member of the American Association of Retired Persons. She is a trustee of the AARP Voter Education Fund and serves on the board's Committee on Member Services and the Advisory Committee on the Health Care Campaign.

Eva Skinner, RN

Her nursing background includes a stint as a clinical coordinator of geriatric services at LA's Cedars-Sinai Medical Center, supervisor of operating rooms in two VA hospitals, and head nurse at New York's Mount Sinai Hospital.

David Blair, MD, a Canadian family physician and long-time activist in organized medicine, will round out the reactor panel. He is current president-elect of the British Columbia Medical Association and former chairman of the BCMA Board's General Assembly.

David Blair, MD

A member of the BCMA's speakers bureau, he talks frequently on a wide variety of issues. Dr. Blair is also a registered pharmacist. He practices medicine in Campbell River, a community on Vancouver Island.

MEETING AT A GLANCE

Washington State Medical Association 1988 Annual Meeting

THURSDAY, SEPTEMBER 15, 1988

7:00 a.m.	COFFEE	*YC-Main Hall*
7:00 a.m.	Registration opens	*YC-Main Hall*
7:30 a.m.	Board of Trustees	*YC-Grand Hall Room A*
Noon	Young Physician Luncheon	*TP-Yakima*
1:30 p.m.	House of Delegates (Opening Session)	*YC-Grand Hall Room C*
3:00 p.m.	COFFEE	*YC-Main Hall*
5:00 p.m.	Fundraiser for Governor Booth Gardner	*To be announced*
5:00 p.m.	WAFP Caucus Reception	*YC-Grand Hall Room B*
6:00 p.m.	HMSS Dinner Meeting	*YC-Grand Hall Room A*
6:00 p.m.	WSPIE Reception/Dinner	*Off site*

FRIDAY, SEPTEMBER 16, 1988

6:30 a.m.	WSSIM Executive Committee Breakfast	*TP-Veranda*
7:00 a.m.	COFFEE	*YC-Grand Hall Room D*
7:00 a.m.	Registration continues	*YC-Grand Hall Room D*
7:00 a.m.	AMA Delegation Breakfast	*TP-Restaurant*
7:00 a.m.	Orthopedics Breakfast	*TP-Yakima*
7:30 a.m.	Reference Committee Orientation	*HI-Rimrock*
7:45 a.m.	ACP/WSSIM	*TP-East Room*
8:00 a.m.	Exhibits open	*YC-Grand Hall Room D*
8:00 a.m.	Special Program – AIDS	*TP-West Room*
8:30 a.m.	Reference Committee A	*HI-Maple Leaf Room A*
8:30 a.m.	Reference Committee B	*HI-Maple Leaf Room B*
8:30 a.m.	Reference Committee C	*HI-Maple Leaf Room C*
8:30 a.m.	Reference Committee D	*HI-Maple Leaf Room D*
8:30 a.m.	Psychiatry	*YC-Grand Hall Room B*
10:00 a.m.	COFFEE	*YC-Grand Hall Room D*
11:30 a.m.	Blood Donor Program	*YC-Main Hall*
Noon	ACP/WSSIM Luncheon	*TP-Garden Terrace*
Noon	WACEP Executive Committee Lunch	*TP-Yakima*
Noon	Psychiatry Luncheon	*HI-Owl Nest*
1:00 p.m.	Emergency Medicine	*TP-Lower*
1:00 p.m.	AIDS Program continues	*TP-West Room*
1:00 p.m.	Psychiatry continues	*YC-Grand Hall Room B*
1:00 p.m.	WSPIE Annual Subscribers Meeting	*HI-Forest*
3:00 p.m.	COFFEE	*YC-Grand Hall Room D*
4:00 p.m.	UW Alumni Reception	*YC-Grand Hall Room A*
5:30 p.m.	Incoming WACEP President's Reception	*TP-Nancy Auer's Suite*
6:30 p.m.	President's Reception and Banquet	*YC-Grand Hall Room C*

SATURDAY, SEPTEMBER 17, 1988

7:00 a.m.	COFFEE	*YC-Grand Hall Room D*
7:00 a.m.	Registration continues	*YC-Grand Hall Room D*
7:00 a.m.	AMA Delegation Breakfast	*TP-Restaurant*
7:00 a.m.	Spokane County Caucus	*HI-Cascade*
7:00 a.m.	Pierce County Caucus	*HI-Suncrest*
7:00 a.m.	King County Caucus	*HI-Lakeside*
7:00 a.m.	Past Presidents' Breakfast	*TP-Yakima*
7:00 a.m.	Early Bird Christian Breakfast	*TP-Veranda*
7:30 a.m.	ACP Breakfast #1	*HI-Maple Leaf Room C*
7:30 a.m.	ACP Breakfast #2	*HI-Rimrock*
8:00 a.m.	Exhibits open	*YC-Grand Hall Room D*
8:00 a.m.	Ophthalmology	*HI-Forest*
8:00 a.m.	Orthopedics	*HI-Maple Leaf Room A*
8:15 a.m.	ACP/WSSIM continues	*TP-East Room*
9:00 a.m.	House of Delegates (Second Session)	*YC-Grand Hall Room C*
10:00 a.m.	COFFEE	*YC-Grand Hall Room D*
11:45 a.m.	Senior Physician Luncheon	*TP-West Room*
Noon	WAMPAC Luncheon	*YC-Grand Hall Rooms A&B*
Noon	Ophthalmology Luncheon	*HI-Rimrock*
1:30 p.m.	House of Delegates reconvenes	*YC-Grand Hall Room C*
2:00 p.m.	WAMPAC Board of Directors	*HI-Suncrest*
3:00 p.m.	COFFEE	*YC-Grand Hall Room D*
6:30 p.m.	New Presidents' Reception	*TP-Garden Terrace*

SUNDAY, SEPTEMBER 18, 1988

7:00 a.m.	COFFEE	*YC-Main Hall*
7:00 a.m.	Spokane County Caucus	*HI-Cascade*
7:00 a.m.	Pierce County Caucus	*HI-Suncrest*
7:00 a.m.	King County Caucus	*HI-Lakeside*
9:00 a.m.	House of Delegates (Closing Session)	*YC-Grand Hall Room C*
9:00 a.m.	Medical Assistants Meeting	*YC-Grand Hall Room A*

Key for locations:
TP – Towne Plaza
YC – Yakima Center
HI – Holiday Inn

For additional information, contact the WSMA at 1-800-552-0612 or (206) 441-9762.

CONTINUING MEDICAL EDUCATION

(Continued from Page 157)

September 9-11—**Fourth Annual Sonography Update and Review Course.** UCSD at Hanalei Hotel, San Diego. Fri-Sun. 17 hrs. $375. Contact: Mary J. Ryals and Associates, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

September 16-18—**Three-Day Seminar in Magnetic Resonance Imaging With Interpretive Workshops.** Los Angeles Radiological Society at Registry Hotel, Universal City. Fri-Sun. 18 hrs. $300. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

October 31-November 4—**13th Annual San Diego Postgraduate Radiology Course.** San Diego Radiology Research and Education Foundation at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $450. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 31-November 1—**San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronada, San Diego. Mon-Tues. 28 hrs. $450. Contact: UCSD.

December 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 13-15—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: R. Dawne Ryals, PO Box 920113, Norcross 30092-0113. (404) 641-9773.

SURGERY

August 18-21—**Discussions of Current Hand Care Concepts.** Plastic Surgery Education Foundation at San Diego. Thurs-Sun. Contact: PSEF, 233 N. Michigan Ave, Suite 1900, Chicago, Illinois 60601.

September 16—**Ultrasonic Liver Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Fri. 8 hrs. Contact: UCD.

September 17—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

October 3-7—**6th Annual Comprehensive Review of Vascular Surgery.** UCLA Miramar Sheraton, Santa Monica. Mon-Fri. 32 hrs. $595. Contact: UCLA.

October 12-14—**Hip and Knee Reconstructive Surgery 1988.** UCLA at Sheraton Princeville Hotel, Kauai, Hawaii. Wed-Fri. Contact: UCLA.

October 29-30—**1988 Regional Review Courses in Hand Surgery.** American Society for Surgery of the Hand at Los Angeles. Sat-Sun. 12 hrs. $200. Contact: ASSH, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

December 3—**Reider Laser YAG & Argon Laser/Brachytherapy Symposium.** Center for Health Education, Long Beach. Sat. 9 hrs. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

December 3—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

December 3—**Cleft Palate Symposium.** UCD at Hyatt Regency Hotel, Sacramento. Sat. Contact: UCD.

January 13-14—**11th Annual Postgraduate Course: What's New in General Surgery.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. Contact: UCD.

OF INTEREST TO ALL PHYSICIANS

August 17-27—**31st Anniversary Postgraduate Refresher Course.** USC at Sheraton Waikiki and Westin Kauai, Hawaii. Wed-Sat. 41 hrs. $535. Contact: USC.

August 18-19—**7th Annual Symposium: General Medicine Update for Practicing Physicians.** Northern Inyo Hospital, Bishop. Thurs-Fri. 10 hrs. Contact: Lynda Schmidt, Northern Inyo Hospital, 105 Pioneer Lane, Bishop 93514. (619) 873-5811.

August 21-31—**31st Anniversary Postgraduate Refresher Course.** USC at Westin Kauai and Mauna Kea, Hawaii. Sun-Wed. 41 hrs. $535. Contact: USC.

August 26-28—**Primary Care Medicine: A Practical Approach.** Scripps Clinic and Research Foundation at Le Meridien Hotel Coronado Island, San Diego. Fri-Sun. 18 hrs. $225. Contact: Bonny A. Mower, Dept of Academic Affairs, 400S, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

September 10—**AIDS: A Practical Approach to Patient Care.** Sutter Health at Sacramento Inn. Sat. 7 hrs. $55. Contact: Sutter Health, Continuing Medical Education, 1111 Howe Ave, Ste 155, Sacramento 95825. (916) 922-6568.

September 15-18—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

September 16-17—**AIDS and the Oncologist.** UCSF at Hotel Nikko, San Francisco. 13 hrs. $225. Contact: UCSF.

September 16-17—**AIDS: A Practical Program Designed for Community Based Physicians.** UCD at Hyatt Regency Hotel, Sacramento. Fri-Sat. Contact: UCD.

September 17—**Treatment Issues With Adult Children of Alcoholics and Co-Alcoholics in Group and Individual Therapy.** Institute for Addiction Studies at Health Education Center, Oakland. Sat. $55. Contact: Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave, Oakland 94609-3081. (415) 652-7000.

September 23-25—**The Medical Office Laboratory: A Technological Revolution in Primary Care.** SDSU at San Diego Princess Resort. Fri-Sun. 18 hrs. Contact: SDSU.

September 24—**Lumbar Spine Disease: A Practical Approach for the Primary Care Practitioner.** Scripps Clinic and Research Foundation at Amphitheater, La Jolla. Sat. 5 hrs. $50. Contact: Bonny A. Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

September 28-30—**Primary Care Medicine: Principles and Practice.** UCSF at the Portman Hotel, San Francisco. Wed-Fri. $365. Contact: UCSF.

October 7-9—**Nutrition.** Center for Health Education at Hyatt Regency, Long Beach. Fri-Sun. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

October 10-14—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 11-14—**Intervention Training.** Monterey Community Hospital Recovery Center, Monterey Conference Center. Tues-Fri. $250. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

October 15-18—**Infectious Diseases: Part I of II.** EPIC Expeditions at Napa Valley. Sun-Tues. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 19-22—**Infectious Diseases: Part II.** EPIC Expeditions at Sonoma Valley. Wed-Sun. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 20-22—**What the Clinician Should Know About the Treatment of Chemical Dependence: A Review and Update for Physicians.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at Los Angeles Airport Marriott. Thurs-Sat. 19 hrs. $350. Contact: Gail Jara, California Society. 3803 Broadway, Oakland 94611. (415) 428-9091.

October 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 25—**Sexual Addiction and Chemical Dependency: The Hidden Connection.** Institute for Addiction Studies at Health Education Center, Oakland. Sat. $55. Contact: Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave, Oakland 94609. (415) 652-7000.

October 27-30—**Clinical Nutrition.** UCD at Sonoma Valley. Thurs-Sun. Contact: UCD.

October 31-November 3—**Intervention Workshop.** McDonald Center for Alcoholism and Drug Addiction Treatment at La Valencia Hotel, La Jolla. Mon-Thurs. 27 hrs. $250. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

November 4-5—**UCD Multi-Specialty Update: Medical Advances of the 80's.** UCD at Sacramento. Fri-Sat. Contact: UCD.

(Continued on Page 161)

CONTINUING MEDICAL EDUCATION

(Continued from Page 160)

November 10-13—**Sexual Literacy: What is it? What do we know? What do we need to know? Whose responsibility is it?** The Society for the Scientific Study of Sex at the Cathedral Hill Hotel, San Francisco. Thurs-Sun. Contact: Bernard Goldstein, San Francisco State University, Biology Dept., 1600 Holloway Ave., San Francisco, 94132. (415) 338-1548.

December 1-3—**American Back Society Fall Symposium on Back Pain.** American Back Society at Hyatt Regency, San Francisco. Thurs-Sat. 19 hrs. Contact: American Back Society, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

December 24-30—**Advances in Medicine.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sat-Fri. 15 hrs. $400. Contact: Joe Harrison, MD, PO Box 10185, Lahaina, Hawaii 96761. (808) 661-8032.

January 19-22—**Health Science Response to Child Maltreatment: 1989.** Children's Hospital & Health Center at Omni Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 20-22—**Urology and Gynecology for Primary Care Physicians.** UCSD at Hyatt Islandia Hotel, San Diego. Fri-Sun. 13 hrs. Contact: Edith S. Bookstein, UREF, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 25-March 4—**Update: Controversies in Emergency and Primary Care.** Scripps Memorial Hospital Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

IDAHO

August 25-27—**Imaging on Lake Coeur d'Alene.** Thurs-Sat. Contact: Kathy Fischer, Spokane, (509) 455-3352.

August 29-30—**Northwest Regional Perinatal Conference—Current Issues in Ob/Gyn, Neonatology and Pediatrics.** Inland Empire Perinatal Center at Coeur d'Alene Resort. Contact: Inland Empire Perinatal Center, 411 Medical Center Bldg, Spokane, WA 99204. (509) 624-3182.

September 2-5—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. 12 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 8-10—**Concepts & Controversies in Perinatal Care.** Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

September 17-18—**NM Chapter, American College of Surgeons Scientific Meeting.** Ramada Classic, Albuquerque. Contact: Dorothy Welby, (505) 266-7868.

September 22-24—**Primary Care Update '88.** UNM Conference Center, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

(Continued on Page 243)

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day. to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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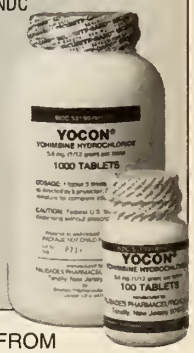

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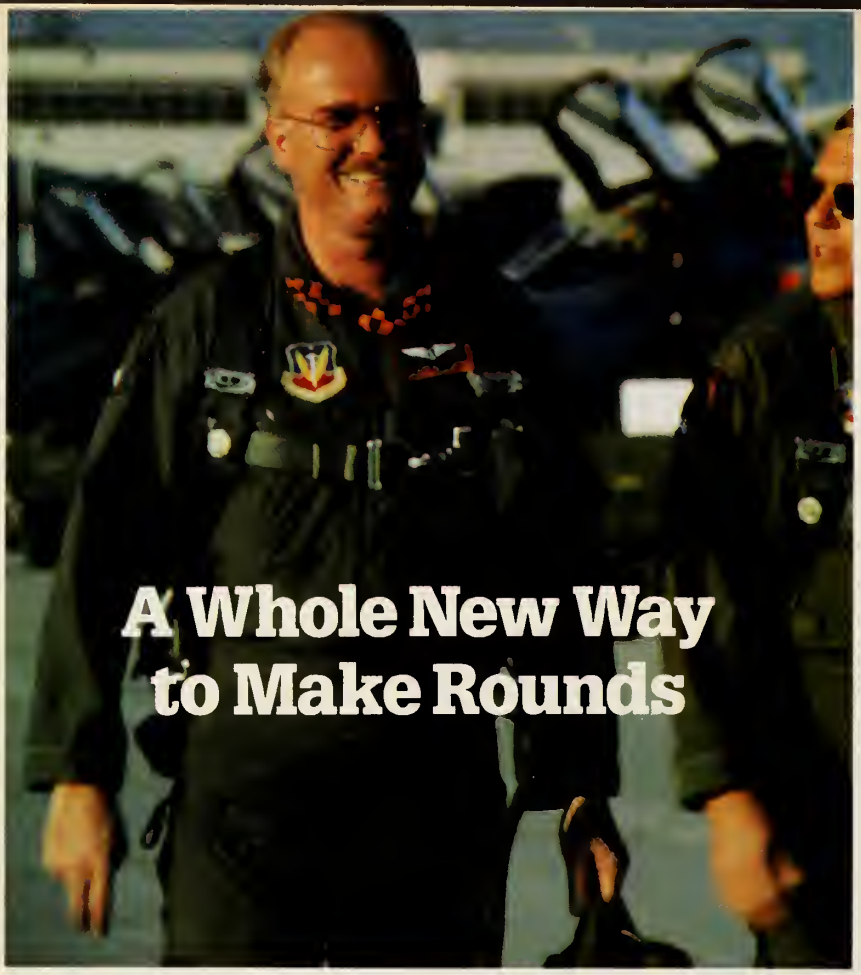

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BRIEF SUMMARY

CONTRAINDICATIONS
There are no known contraindications to the use of sucralfate

PRECAUTIONS
Duodenal ulcer is a chronic, recurrent disease While short-term treatment with sucralfate can result in complete healing of the ulcer, a successful course of treatment with sucralfate should not be expected to alter the post-healing frequency or severity of duodenal ulceration

Drug Interactions: Animal studies have shown that simultaneous administration of CARAFATE (sucralfate) with tetracycline, phenytoin, digoxin, or cimetidine will result in a statistically significant reduction in the bioavailability of these agents The bioavailability of these agents may be restored simply by separating the administration of these agents from that of CARAFATE by two hours. This interaction appears to be nonsystemic in origin, presumably resulting from these agents being bound by CARAFATE in the gastrointestinal tract. The clinical significance of these animal studies is yet to be defined However, because of the potential of CARAFATE to alter the absorption of some drugs from the gastrointestinal tract, the separate administration of CARAFATE from that of other agents should be considered when alterations in bioavailability are felt to be critical for concomitantly administered drugs

Carcinogenesis, Mutagenesis, Impairment of Fertility: Chronic oral toxicity studies of 24 months' duration were conducted in mice and rats at doses up to 1 gm/kg (12 times the human dose). There was no evidence of drug-related tumorigenicity A reproduction study in rats at doses up to 38 times the human dose did not reveal any indication of fertility impairment Mutagenicity studies were not conducted

Pregnancy: Teratogenic effects Pregnancy Category B Teratogenicity studies have been performed in mice, rats, and rabbits at doses up to 50 times the human dose and have revealed no evidence of harm to the fetus due to sucralfate There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers: It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised when sucralfate is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS
Adverse reactions to sucralfate in clinical trials were minor and only rarely led to discontinuation of the drug In studies involving over 2,500 patients treated with sucralfate, adverse effects were reported in 121 (4 7%)

Constipation was the most frequent complaint (2 2%) Other adverse effects, reported in no more than one of every 350 patients, were diarrhea, nausea, gastric discomfort, indigestion, dry mouth, rash, pruritus, back pain, dizziness, sleepiness, and vertigo

OVERDOSAGE
There is no experience in humans with overdosage Acute oral toxicity studies in animals, however, using doses up to 12 gm/kg body weight, could not find a lethal dose Risks associated with overdosage should, therefore, be minimal

DOSAGE AND ADMINISTRATION
The recommended adult oral dosage for duodenal ulcer is 1 gm four times a day on an empty stomach

Antacids may be prescribed as needed for relief of pain but should not be taken within one-half hour before or after sucralfate

While healing with sucralfate may occur during the first week or two, treatment should be continued for 4 to 8 weeks unless healing has been demonstrated by x-ray or endoscopic examination

HOW SUPPLIED
CARAFATE (sucralfate) 1-gm tablets are supplied in bottles of 100 (NDC 0088-1712-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1712-49) Light pink scored oblong tablets are embossed with CARAFATE on one side and 1712 bracketed by C's on the other

Issued 1 '87

Reference:
1 Eliakim R, Ophir M, Rachmilewitz D *J Clin Gastroenterol* 1987, 9(4) 395-399

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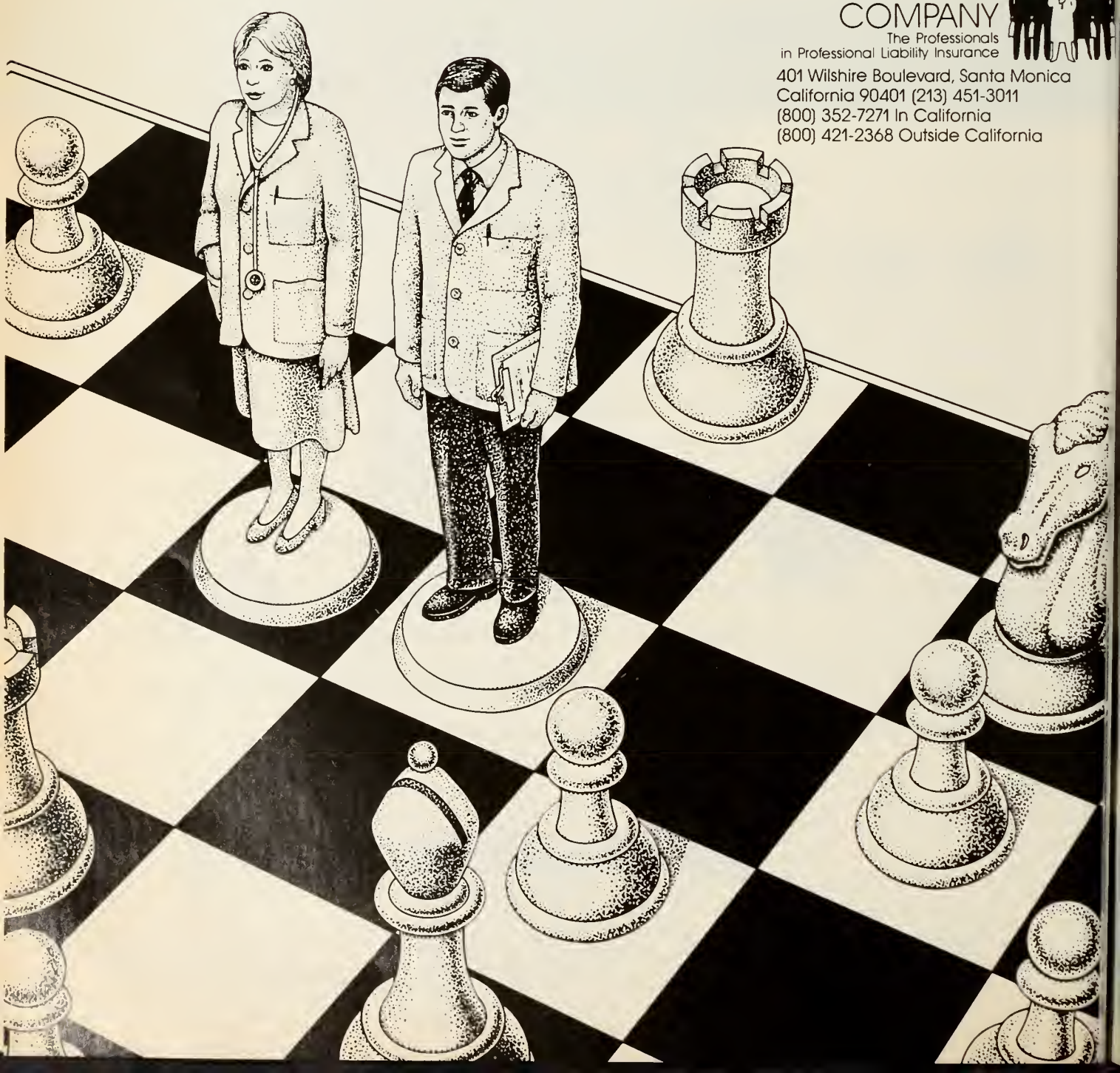
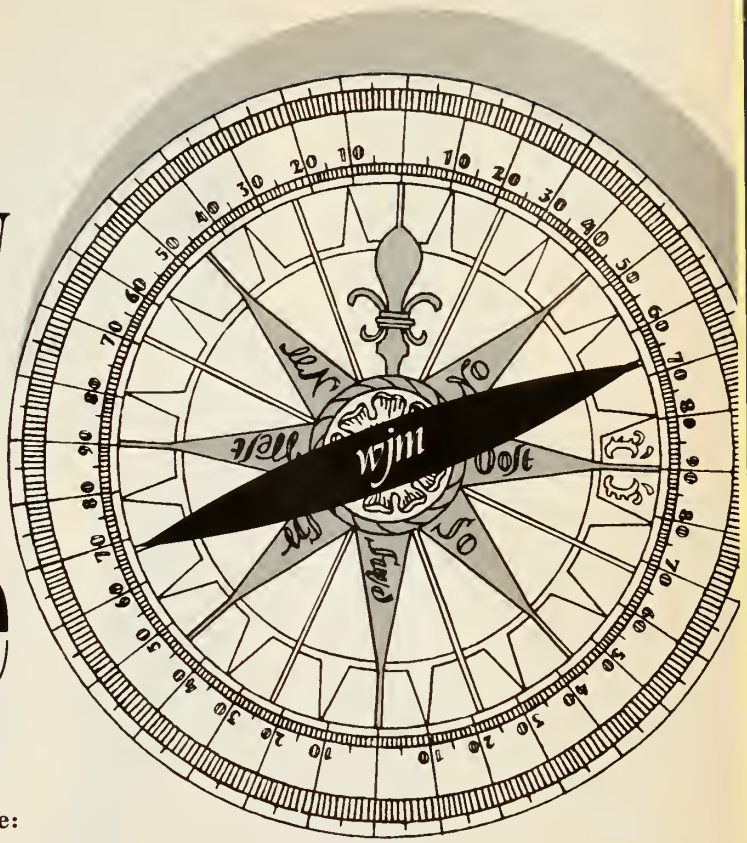


the new DIRECTIONS in medicine



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* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.*
Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. *If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake.* ***Associated widened QRS complex or arrhythmia requires prompt additional therapy.*** *Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.*
Precautions: *The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin[ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.*
Adverse Reactions: *Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.*
Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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Finding Something Good In Everything

Marshall B. Block, M.D.

On a recent visit to Arizona, I was sitting with my father and noticed that he had aged. He had lost weight. His skin was wrinkled. He walked with a stoop, I had to talk louder, and he seemed to be more interested in what he had to say than what others were expressing. I noticed that he was wearing a shirt that had a frayed collar, and had old stains which previous attempts to remove had been unsuccessful. I asked him why he was still wearing the shirt even though it was stained and frayed. He looked at his shirt, then looked at me and pointed to the buttons, "They're still good!" I think he was saying that perhaps function is more important than appearance.

How often do patients arrive in our office complaining about their previous encounter with a physician? It appears to be an ever increasing problem faced by grievance committees and boards of medical examiners. If queried, the patients would rant and rave about various things that went wrong with their previous relationships, either with the physician himself or the office staff.

Medical consulting services take advantage of "exit surveys" to formulate helpful hints for physicians in their offices. We shouldn't make patients wait. We shouldn't overbook. We should be well groomed. We should all wear white coats. We should have pleasant and pleasing reading material in our waiting rooms, and our office staff should be smiling. We should be frequently washing our hands and above all, we should be spending a large amount of time with each patient discussing all of their needs; medical, social, emotional and financial. In the real world, it is impossible to accomplish these idealized goals. Some of us come close on occasion with some of our patients, but many times we fall short. The appearance of our offices and staff and ourselves can't be perfect all the time. Some medical practices see patients for prolonged periods of time while others tend to see new patients fleetingly and in great numbers. The nature of the practice dictates to a great extent the kind of ambience that exists within each individual office setting. Although initial appearances may be impressive to the patient, it is the medical care ultimately rendered which is of crucial importance to their well-being. Patients respond to a number of cures in our environment which can make or break a therapeutic relationship and consideration to some of these factors may prove mutually beneficial.

It is more important to have buttons on your shirt than a shirt without stains. ❑

Marshall B. Block, M.D., Editor

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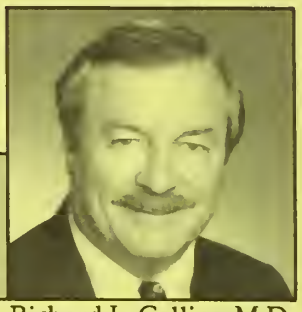
- Classified Advertising

From Our President



Richard L. Collins, M.D.

Inaugural Address
Richard L. Collins, M.D., President, Arizona Medical Association
June 10, 1988--Loews Ventana Canyon Resort--Tucson, Arizona

If there is a message in this, it is embodied in the title--"The State of the Association."

We have a number of lofty goals engraved on the certificate which hangs in the hallway of our headquarters and we have some responsibilities outlined in our bylaws. But if a member–or more to the point, a non-member we are trying to recruit–asks you what good the Arizona Medical Association has done for the medical profession or for the public in general, would you know the answer? I am going to try to answer that question this morning, because I believe that that is the guts of ArMA. We do act in ways that represent the medical profession and act in ways to assure public access to affordable quality medical care.

ArMA is organized so that it can work towards its goals in two ways. First, through its volunteer committee structures, and second, through the activities of its professional staff. Let's look at the committees as defined in the bylaws and see if they are doing their share to meet ArMA's stated organizational goals. We do not always hear much about the committees because all too often the members of our committees are the proverbial unsung heroes. But the members do devote mucho hours and energy helping to meet their responsibilities and solving the problems confronting the Association.

Let's take the goals one at a time.

Goal One is to promote optimum health and medical service for the citizens of Arizona. Our Committees on Medical Service, Scientific Affairs, and Maternal and Child Health Care all contribute toward our success in meeting this goal.

The Committee on Medical Service, chaired by Jane Orient, M.D., last year and Len Kirschner, M.D., this coming year, studies both the social and economic aspects of medical care and it suggests ways to develop new or expanded services to meet society's changing needs. Recent examples of the committee's activities include its study and involvement in the controversy involving the future of the Arizona Health Care Cost Containment System (AHCCCS). The committee adopted a position of recommending continuation of the AHCCCS program through September of 1989. This position was adopted at a time when the federal government was considering phasing out the AHCCCS program because of the controversy related to financial responsibility for reservation Indians. The feeling of the committee was that without a workable alternative it is not in the best interest of the citizens of Arizona to dismantle AHCCCS. This issue is far from solved.

The Committee on Scientific Affairs, through its Sports Medicine Subcommittee chaired by Robert O. Wilson, M.D., plays a major role in ArMA's success in meeting Goal Number One. Not only have they produced fourteen consecutive annual Sports Medicine Symposia dealing with the most current issues and problems facing the sports medicine community, but their work has lead to other landmarks as well.

continued on Page 8

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Stress In Medical Education

In March, 1980, Dr. Murray DeArmond, Director of Student Health Service at the University of Arizona wrote an excellent article, "Stress Among Medical Students," which was published in Arizona Medicine. It was perceptive, sensitive, articulate, and informative. Why have we chosen "Stress in Medical Education" as the topic for this month's journal? The stresses Dr. DeArmond wrote about are still present, and critical, and new stresses have added to the old ones. We need to be aware of these burdens--and help with their coping.

Young Adult Development

The majority of students face the developmental tasks of young adults, which include establishment of ego and sexual identities, detachment from parents, development of independence, pursuit of vocational goals, development of an occupational identity, and achieve a capacity for intimacy. The demands and stresses of medical education often interfere with the successful completion of these tasks. Excessive time demands, the extraordinary volume of information to be learned, the programmed prolonged adolescence, and the intense competition among highly qualified over-achievers, may interfere with healthy development. Such traits as devotion to duty, compulsiveness, obsessiveness, personal insecurity, isolationism, and competitiveness common to those selecting medicine reinforce the stressors. The resultant development of maladjusted adults is not unexpected; however, the majority seem to survive reasonably intact and is a tribute to human resiliency.

Older Students

Older students are now added to the student pool, adding to the other problems. Many have families; many have been successful in other careers. They have completed the developmental tasks of young adulthood, but are forced back in time to deal with many unanswered questions--and are surrounded with a younger peer group dealing with its own problems. Their struggle is often more isolated and lonely than is that of younger students.

Women and Minorities

The last decade has seen a virtual explosion of the number of women and minorities entering medicine. A woman still must face the major stress of the inevitable ticking of the biological clock plus the above noted developmental tasks. Medicine is a male-dominated profession, with few positive female role models. Women in medical school report more loneliness and isolation than male students. Minorities feel these same stresses as well as educational, cultural and ethnic differences. These individuals may feel isolated by their classmates, and fear they are not perceived as equals.

Cost of Health Care

The tremendous growth in technology in the past decade has achieved 'miracles' for many patients. Organ transplants, multiple interventions for ischemic cardiac disease, prenatal diagnoses and treatment--the developments and progress have been staggering. Of course, these are expensive developments which have increased the cost of health care to prohibitive levels. Attempts to control costs have led to markedly changing reimbursement and health insurance plans--all which have affected the lifestyles of present and future physicians. All the discussion and gloom suggesting decreased fiscal rewards for physicians serve as an added stress on students whose debts mount to record heights.

Ethics

An even greater stressor is the ethical dilemma such advances evoke. Who gets what? How can we provide health care for all people, when the costs can be staggering? Who decides which patient lives and which dies? And who will insure the decision maker--and protect him/her from the malpractice attorneys? How will these young physicians protect themselves from AIDS; more realistically, how will they protect themselves from the fear of AIDS, and still provide competent and compassionate care to the virus' victims? Is the risk worth the gain?

What Can Be Done

The first step in dealing with the problem of continued on page 12

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Electronic Information For Physicians: A New Dimension In Solving Traditional Problems

Part II

Last time, the capabilities of AMA/NET to assist with diagnostic and therapeutic problems were discussed.

III. Current Awareness of Specific Medical Topics

Physicians often need to obtain the latest information in a particular medical subject area. This may be a particular disease state, subspecialty, or a topic of current interest. Traditional sources for such information are the many available medical news publications, scientific meetings, and current medical literature. However, it is often very difficult to sort through the plethora of available information to find the specific items of interest.

This is another area where electronic information can be helpful. AMA/NET provides a number of services which directly address the need for current medical information. One of the most useful of these is the Associated Press Medical News Service, which provides up to the minute reports of medical news as they are transmitted on the Associated Press newswire. These stories are updated continuously, and are available on both a chronologic basis and by subject area. Medical news stories are thus available almost immediately on AMA/NET.

Another useful source of current information is the literature update by specialty. This provides, via a search of EMPIRES, the most recent literature in a given specialty area. The social and economic aspects of medicine (SEAM) database, which is maintained by the AMA, is another useful source of information. This database references selected articles in both medical and non-medical literature which pertain to social, ethical, and legal issues related to the practice of medicine. Topics of current controversy are often represented in this database.

These sources of information, combined with the literature searching capabilities, make it easy to obtain the latest information on any particular topic of medical interest.

IV. Reference Information

Reference information needed by physicians is traditionally available through a nearby medical library. An example of this type of information on AMA/NET is the CPT procedure codes. The CPT codes are used for reporting most medical procedures to third party payers. This can be useful when such a code is needed and the printed reference is not available.

V. Continuing Medical Education

Continuing medical education has become increasingly important as the rapid pace of medical discovery leads to proliferation of new knowledge and changes in previous concepts. The traditional methods for obtaining continuing education involve attending meetings, either locally or by traveling to a remote location, or reading material followed by subsequent self-administered examinations. More recently, CME has been available in videotape form.

Electronic information has a role to play in CME, also. In particular, computers are well suited for patient simulation type of exercise where the effects of many different patient management scenarios can be explored safely and easily. AMA/NET provides access to a number of such simulations which have been developed at the Massachusetts General Hospital. Examples of these include abdominal pain, diabetic ketoacidosis, and hypertensive emergencies. With these programs, access to electronic information can provide new opportunities in continuing medical education.

VI. Communications With Colleagues

Traditionally, physicians' communication with their colleagues has consisted of scheduled meetings, either local or remote, chance meetings in the hallway ("curbside consults"), telephone communication (which is very inefficient), and communication by letter, which is frequently used to report the results of patient referrals.

AMA/NET provides access to a new form of electronic communication: electronic mail.

With electronic mail, messages are sent immediately, but stored so that their convenience. This greatly simplifies written communication with colleagues since sender and receiver do not need to be simultaneously available. Thus, electronic mail can provide the speed of the telephone without the associated inconvenience and delay, and represents a cure for chronic telephone tag.

Electronic communication can also take the form of an electronic bulletin board, allowing announcements to be made which are immediately accessible to system users.

VII. Non-Medical Information

Physicians also need information that is not medically related. Obviously, there are a multitude of traditional sources for all types of information via newspapers, magazines, other periodicals, and television. Electronic information provides a supplement to these sources. In particular, AMA/NET provides on-line access to the Official Airline Guide, which is very useful in planning travel, as well as various types of financial information. The latter includes business press releases, financial and commodity news, tax notes, and stock and commodity quotations. It is also possible to obtain information about investments managed by AMA Advisers.

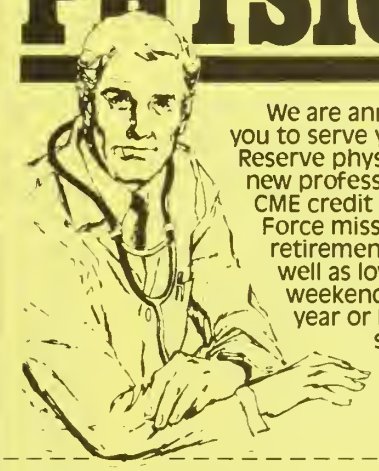
VIII. Conclusions

Electronic access to information provides an important adjunct to traditional methods. In some cases electronic information provides capabilities which are not otherwise available. In the future, new forms of electronic information will be available. One such form is the "interactive reference," which provides reference information tailored to an individual patient's situation. With such a reference, the process of extracting information relative to a specific patient from a number of sources is performed automatically providing convenience and time savings.

This report has described some of the information sources and capabilities available on AMA/NET. It is clear that physician access to electronic information greatly expands, but does not replace, traditional information access methods. ❑

William A. Yasnoff, M.D., Ph.D.

PHYSICIANS



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A GREAT WAY TO SERVE

Continued from page 2

They fostered the creation of Basic Athletic Sports Injury Care program which has become a national model for training coaches and other athletic program supervisors both in what to do and what not to do in the intensive first aid when athletes are injured on the playing field. Working with ArMA's lobbyist, they were instrumental in the passage of "Good Samaritan" legislation, protecting volunteer physicians serving as school or community team doctors. They have promoted the hiring of certified athletic trainers in the state's high schools, established a standard statewide basic equipment list for all athletic events and youth sport programs, and developed a standardized form for all school athletic physical exams.

On the drawing board is a very special program which will, also, substantially contribute towards promoting the health and medical services for Arizona citizens and avoid the mandated solution used in the Peoples Republic of Massachusetts. Its working title is the ArMA V.I.P. (Very Important Patient) Program and it is hoped it will provide medical services for that group of senior citizens who have too much income to qualify for AHCCCS and too little income to be able to afford food, clothing, shelter and medical care. The committee developing Arizona's version of this concept which has proven itself in dozens of other parts of the country, chaired by Frank Loffer, M.D., has surveyed our members to find out whether they would be interested in participating in such a program if the logistics could be worked out. The response has been heartwarming with only a fraction of the responses returning in the negative. I am sure you will be hearing a lot more about this program in the months to come as the Committee works out the "nuts and bolts" to make it a practical answer to the problems among Arizona senior citizens. With 87% of ArMA's members responding favorably, the "not interested" group were retired, pediatricians and physicians who already accept assignment for the most part.

The Committee on Maternal and Child Health Care, most recently chaired by Joe Daily, M.D., and to be chaired by Larry Linkner, M.D., is, by virtue of its title, concerned with the health and well-being of a very important segment of the Arizona population--mothers and babies. The committee, among other things, has been diligently working on developing a statewide data base for studying infant mortality and morbidity, attempting to address concerns regarding early "access" to care by pregnant women, and is involved in planning for establishing a state placental registry.

If I may repeat Goal Number One, it is to promote optimum health and medical services for the citizens of Arizona. I am speaking about ArMA but right here at Goal Number One is our Auxiliary. It may have been neutered but it is still potent. The Auxiliary has sponsored workshops for its members, distributed informational booklets--our message information--to elementary schools, collected signatures for 103, collected donations for ArMPAC, informed the elderly, financed the hotline, are huge supporters of AMA-ERF, and have been our dearest friends.

Everybody benefits from the "GEMS" program (Good Emergency Mother Substitutes) and the Human Adventure Center and "TAM" (The Transparent Anatomical Mannequin). Most of us do not know that Mohave and Yavapai and Yuma give scholarships to nursing students or that Coconino supports the Sunshine Rescue Mission, that Pinal, Maricopa and Pima are active in chemical abuse programs.

Goal Two is to determine the most effective organizational structure and communication mechanism for our Association. It is self-evident to this group that you have been deeply involved in the organizational structure related to this goal, particularly in the establishment of our newest section devoted to the Young Physicians and in consideration of the best ways to involve both employed physicians and foreign medical school graduates in the mainstream of organized medicine. There is no place in an organization like ArMA for "an activist for the status quo."

The Committee on Long Range Planning, always chaired by the Vice President–last year by Mark Ivey, M.D.--is working on improvement of internal communication by the decision makers, probably with a computer oriented telecommunication network. This is under active investigation.

We are all aware of the three legs of an organization stool. They are first the organizational structure, secondly the budget and thirdly the timetable. We have addressed the organizational structure. The budget is the responsibility of the Committee on Finance and is the responsibility of our Treasurer, Bob Brooks, M.D. It is a critical part of ArMA's success in meeting Goal Number Two. For your information, ArMA's budget is $1,524,455.00 or over one and one half million dollars. Not all of that goes to a president's expense account.

Another step towards this goal was authorized by the Executive Committee and carried out by staff over a year ago. That was a major survey of the membership to find out how they felt about programs and services ArMA offers, which ones were valuable and should be continued or expanded and which ones are of little interest and should no longer be promoted. Many of the decisions to expand or delete programs and services in the past year have been based on your opinions expressed in that survey. At the same time, non-members were surveyed also and much of our present emphasis in our new membership recruitment information is based on the interest and needs of non-members expressed in response to that survey.

Goal Three is to represent the entire medical profession, including medical students, in Arizona; such representation to include but not be limited to being the advocate of the membership with the legislative, administrative and judicial arms of state government. The most intensely involved committee contributing towards success in meeting this goal is the Committee on Legislative and Governmental Affairs, which

during late winter and spring spends countless hours reviewing all of the proposed or pending legislation which may affect the health care of the community and then makes recommendations for ArMA's lobbying efforts. On a year round basis, this committee monitors the development of state regulations which may affect the medical community and makes appropriate recommendations for action to the ArMA Board. We are guided most adroitly, both past and future, by Bill Mangold, M.D.

Because of the unusual political climate this past year, more was achieved on defense than offense, notably:

* allowing citizens to order their own lab tests
* expansion in scope of practice for optometrists
* defining chiropractors as "Primary Care Physicians"
* licensure of homeopathic-physician's assistants
* mandatory premarital AIDS testing

Similarly, the Committee on Professional Liability represents the Association in the establishment of professional relations with insurers, and other organizations involved in official action which impacts on liability issues.

This committee was instrumental in starting a task force on medical liability which has, under active investigation and consideration, multiple approaches.

1. If the present tort system is going to be the working legal vehicle then constitutional change is mandatory. Even the most conservative constitutional protector will have to admit that our constitution is flawed. Presently, the Arizona Constitution does not allow a woman to be Governor and, if a Governor is impeached, there are several unanswered questions. Our constitution was the 48th written and done so in a very progressive political climate. There have been over 100 changes already made in the Arizona Constitution. One more will help keep it a living document.

2. Tort change is being sought with or without constitutional change even though the effect is questionable. I point specifically to the achievement in changing joint and several liability to just several liability.

3. Most importantly, however, is probably going to be the alternate dispute resolution mechanisms. It may be that a patient could contract with his physician and thereby take their relationship out of tort law and into contract law. The reference is *Salt River Project vs. Westinghouse* with a window being opened by none other than Justice Feldman who noted that this effectively might be voluntary tort limitation.

Importantly, contract law is not constitutional law but common law and contract law can be amended by statute. We already have a sample contract between health care provider and patient providing for discounts in the price of medical care in exchange for certain limitations upon recovery in the event of medical malpractice claims, as well as a proposed statute endorsing this type of agreement as consistent with public policy of the state.

4. Considered, also, was a no-fault based administrative plan similar to the Industrial Commission where the liability limitation would be a swap for a fee schedule.

5. And, probably not last, is the most active, a fault based plan called C.A.R.E., standing for "Compensation And Rehabilitation Effort." The task force is working toward a constitutional amendment which would allow the Legislature to establish a more direct, fair, economical and efficient system for compensating patients injured as a result of inappropriate medical treatment.

Goal Four is to expand ArMA's role in promoting the standards and clarifying the scope of medical ethics. At the present time, any complaints about Maricopa physicians are referred to the Maricopa County Medical Society and complaints about Pima physicians are referred to the Pima County Medical Society--both have Grievance Committees and handle those issues directly by choice and request. Last year the Committee on Professional Affairs was chaired by Neil Ward, M.D., and will be again this year. Subcommittees of the Committee on Professional Affairs also have been active in providing services to physicians which contribute to achieving this goal.

The Physicians's Health Subcommittee, led by Don Damstra, M.D., deals directly with the impaired physician who grapples with substance abuse or psychological problems. Recent action by the State Legislature has made it possible for the Physician's Health Program sponsored by the subcommittee to become perpetually self-funding through a percent of the licensing fee charged by the Arizona Board of Medical Examiners. This was a joint effort by ArMA and BOMEX. Intervention and appropriate treatment has saved hundreds of Arizona physicians who otherwise might have inadvertently provided inadequate patient care or as a result been permanently barred from the practice of medicine.

Three new subcommittees have been established within the last year. The Physician Support Subcommittee, guided by Joe Hanss, M.D., is made up of physicians who know the liability lawsuit process and know the pressures and problems involved. Their goal is to reach physicians being sued so support can be offered, to help physicians handle their stress experienced during the litigation process, and to provide technical information about the litigation process itself including its too often ill-explained perils and pitfalls. They are meeting twice this month with instructional sessions on the legal and psychiatric aspects of malpractice suits. While the committee cannot yet evaluate the actual facts of the case without risk of being subpoenaed as a witness during the trial, the committee's attorneys have looked at methods of protecting confidentiality. If this can be done, discussions between defendant and the support group could not be subpoenaed by the court.

The second new subcommittee is Review Oversight chaired by Sierra Vista's Robert M. Anderson, M.D. It was established to provide a mechanism for reviewing peer review. As more and more reviewing is being done, it was felt by our Board that the chances for inappropriate review are increasing and

there is a need for support for physicians who have been inappropriately reviewed. While stressing that appropriate review is a valid part of the process which encourages high standards and quality medical care, the committee has established objectives for dealing with inadequate review or the flaws in the review system which has led to inappropriate review. In essence, this is reviewing the reviewer's review for oversights.

Interest in small area analysis in 1986 resulted in a formal application by ArMA for grant funds to become involved in this activity. The request for funds was ultimately denied. Subsequently, as a pilot project and in cooperation with HSAG, a small group was formed to look at the statistics developed by Medicare on transurethral prostectomy. The group, known as the Turp Study Group, under chairmanship of Clyde Kurtz, M.D., has been meeting since late 1987. Some very interesting trends in health care have surfaced, and a report on conclusions reached is expected soon. It is possible this activity may be expanded into study of other procedures in the future.

Goal Five is to provide individual members with benefits and services to aid in their professional pursuits. This is truly an area in which ArMA shines. If one asks the question what is in it for me, this is the answer. This is what you can say when trying to recruit new members to the Association. In addition to basic services, such as patient referral, practice management and workshop, printing and updated information through regular publications, ArMA has established two subsidiaries which provide financial and insurance service to members.

Another "win-win" situation inherent in ArMA membership is quality service and extremely competitive pricing in regards to insurance and investment services available through our subsidiaries. I have recently taken the time to personally examine the brokerage and money management services from the perspective of a potential customer; and I am delighted to pass along to you that the service is first rate in every respect and I am proud to say that I now do business with ArMA Financial Services.

While I was in the Financial Services/Membership Benefits offices, I learned a little bit about why it <u>really</u> makes sense to do business with our own store. For example, a colleague of mine age 51, was carrying a $5,000 per month disability income policy with an annual premium of $3,582. When he compared that policy to the Monarch Life Policy endorsed by ArMA, he found that a much better policy is available with an annual premium of $2,975. The savings is over 17% for better coverage.

Similarly, term insurance available through ArMA Membership Benefits is often 20-30 percent less expensive, all written by A+ carriers. The revenue potential to the Association is staggering, and it is money that we would put out to those who care nothing about improving medicine.

For those of us who are perhaps more investment oriented, I find it reassuring to know that, in an actual case history, ArMA Financial Services was able to provide a defined benefit plan termination and rollover of assets to a profit sharing plan for one-third the charges proposed by outside legal and actuarial firms. Less money spent on fees naturally means more money actually invested!

In the area of management fees and commissions, during calendar 1987, ArMA Financial Services managed a fairly typical $140,000 account for less than 1%, while other management would have resulted in expenses of 2.5%. I do not know about you, but the $2,600 is a real plus to me.

Think of it--we own a broker/dealership which provides:

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Let's face it, part of meeting the economic challenges which face us as physicians today, is to take advantage of every opportunity to work <u>together</u> to use our resources efficiently and effectively. Our Association membership entitles us to tangible advantages. Let's at least give our subsidiaries a fair chance to <u>earn</u> our support!

ArMA Financial Services provides a variety of pension plans and investment products for which costs are substantially reduced by ArMA's salaried staff whose number one priority is our members' best interest. Areas of expertise include stocks and bonds, IRA's and Keogh's, mutual funds and trusts, a benefit trust and profit-sharing plans.

ArMA Membership Benefits is a full-service insurance department which has negotiated extremely beneficial life, health and disability insurance terms exclusively for ArMA members. Plans packaged to provide appropriate benefit amounts and protection with the highest quality of service and products at the lowest price.

Under investigation is a multiple employer benefit plan and trust. This is an attempt to approach the liability insurance tail costs if the system stays in its present horrible disarray. There may be a way to prepay tail coverage with pre-tax dollars. Our attorneys would cringe if I described it as being very similar to a pension and profit-sharing plan, except that its purpose is not retirement but to establish severance pay which would cover tail costs. Also, it may not be available to creditors because the trust would be subject to forfeiture by death, age 70, etc.

Public support is also essential to protect physicians' professional performance. ArMA's positive relationship and regular two-way communication with the mass media lets the public know what is happening in the health care community and shares physicians' concerns so everybody can understand the crises threatening health care quality.

Goal Six is to represent membership in matters pertaining to the economics of medicine. A standard was set for ArMA actions toward meeting this goal when the Association faced the liability insurance

availability crisis in the mid-1970's and became the founder of the Mutual Insurance Company of Arizona (MICA), the state's non-profit physician-owned provider of malpractice policies.

Since that time, ArMA has tracked the liability crisis through its Committee on Professional Liability which is charged with establishing relationships with insurers, the Bar and the Legislature and public to reduce professional liability risks and losses. The committee works closely with ArMA's Committee on Legislative and Governmental Services to promote appropriate action by the state lawmaking bodies. Last year's chairman agreed to continue again; that is Ed Sattenspiel, M.D.

At the same time that the Committee on Professional Liability was establishing the CARE Task Force, our Executive Committee and Board of Directors authorized and actuarial audit of the policies and procedures used by MICA to set rates for liability insurance policies with current decibel levels of criticism of insurance companies accused of being responsible for the liability crisis now confronting all of us. ArMA's leadership wanted to have unassailable information as to whether MICA's skyrocketing rates were really necessary. The national consulting firm of Tillinghast was contracted to perform an independent review of MICA's rates and rate setting process on behalf of ArMA members. The results as we all now know clearly show that MICA's rates were at the minimal levels necessary to ensure its financial ability to meet its responsibilities to its rate payers and pay claims in the years to come. The results also show that MICA was not the problem causing the present liability crisis and that the civil tort system was broken, and until its problems are addressed, the crisis will continue.

The real increase that MICA needed to maintain a status, i.e., its reserves, would have been a 49% premium rate increase. MICA did not feel that the physicians would swallow that increase and consequently applied only for a 33% premium increase. They managed to reduce the increase by dipping into their reserves. To me that is like mortgaging capital equipment for operating expenses and, if that kind of approach is repeated very often, I could foresee MICA becoming insolvent.

MICA has stated unequivocally that they will roll back premiums 5% if a periodic payment bill is passed and signed into law. To date it has not happened; but we are still working on it.

The Tillinghast report has been defiled by those who accuse the rip-off insurance companies--and everyone but themselves--as being the whole cause of the liability crisis. In fact, the Tillinghast audit stands among at least four audits all coming to the same general conclusion. There are three national firms and the State Department of Insurance whose reputations are at variance with anecdotal analysis. Let those who look to the stars for answers look to themselves. If the truth is ugly, it's an ugly truth.

Goal Seven, the last but far from the least on the list, is to represent the membership in matters pertaining to medical education, scientific affairs, and the promotion of the art and science of medicine.

The Committee on Medical Education, chaired by Charles Trahern, M.D., both last year and this year, has been instrumental in helping the Association achieve this goal. ArMA is the sole Arizona entity authorized by the National Accreditation Counsel for Continuing Medical Education (ACCME) to approve institutions and organizations to sponsor Continuing Medical Education programs. The committee's year round responsibility is to survey, evaluate and accredit hospitals and medically oriented organizations to offer Category One Continuing Medical Education programs.

In addition, the Committee sponsors three other major projects which promote medical education and scientific affairs. First is the Continuing Medical Education program held in conjunction with ArMA's annual meeting each June and at three other times during the year. In order to be sure that this year's topics were what the members really wanted and needed, the committee surveyed the membership and asked them what they wanted on the program. This year's CME at the annual meeting is a direct response to that survey result. What people said they wanted is exactly what they got.

The second project which fosters medical education and scientific affairs is aimed at promoting accurate public understanding of medical issues. The program is ArMA's Annual Media Awards competition, which provides recognition to radio, television, newspaper, high school and college reporters who have produced outstanding articles or radio or T.V. tape dealing with medical topics.

The third project is the committee's annual scholarship awards given to carefully selected medical school students from Arizona.

The Committee on Scientific Affairs also contributed greatly to Goal Number Seven with its intense committee work which drafted the Association's first official policy recommendations regarding Acquired Immune Deficiency Syndrome (AIDS). Their policy recommendations covered both mandatory and recommended testing, informed consent, reporting requirements and the use of data, legal and insurance issues, public education and treatment recommendations.

The Committee on Scientific Affairs doing this work was chaired by Bob Westfall, M.D., last year and will be chaired by Steve Englender, M.D., this coming year.

I do not think there is any doubt, that given the resources available, ArMA has more than met its responsibilities under the bylaws and has effectively worked toward its goals in an exemplary fashion. We can, however, always be more effective and reduce our limitations. To do so, we must be organized; we must have a realistic budget; and we must have a pragmatic timetable for action. And we cannot work in a vacuum. Active cooperation between ArMA and both the AMA and our county medical societies--unified and non-unified--is essential to our pursuit of effectiveness. This does not mean we must always agree; certainly not. When two

President's Message Continued from page 11

people or two organizations or two entities of any sort are in perpetual agreement, it only means that only one of them is doing the thinking. I heard a lovely phrase the other day which describes what I am talking about. "It is the friction between the bow and the strings which makes the violin sing." In our communications and in our contrasting views, we can learn more from each other and make much progress towards improving our effectiveness as we continue to pursue our goals.

In my opinion, this is the State of the Association ❑

Richard L. Collins, M.D.

Dean 's Editorial continued from page 4

stress in medical education is to acknowledge the problem exists. We need to validate the concerns of the students, and "give permission" for them to talk about their feelings without being made to feel weak and unworthy of medicine. This should be done as part of the formal curriculum of the school: seminars, workshops, discussion groups on recognizing and coping with stress.

Having acknowledged the problems, we need to provide the necessary resources to help students deal with them. Personal counseling, peer counseling, peer support groups, and training for faculty members in recognition and referral of stressed students should be available to all students. In addition, formal referral to psychiatrists and psychologists in the community should be facilitated by the student health service or other appropriate faculty and staff.

Serious consideration should be given to re-evaluating the current system of training medical students. Earlier patient contact; small group teaching and discussion--aimed at integrating basic science, clinical science, and personal, emotional aspects of patient care--should be a key element of the process. Feelings are real, just as real as science, and need to be addressed.

The challenge to medical educators is to guide these students through their critical developmental years, and at the same time stimulate them with the challenge, excitement, and joy of medical practice. The true rewards of medical practice are still present--the gratitude and respect of those patients behind the closed doors of the clinic rooms. ❑

Larry Moher, M.D.
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Corrections in July issue. Should read as follows:

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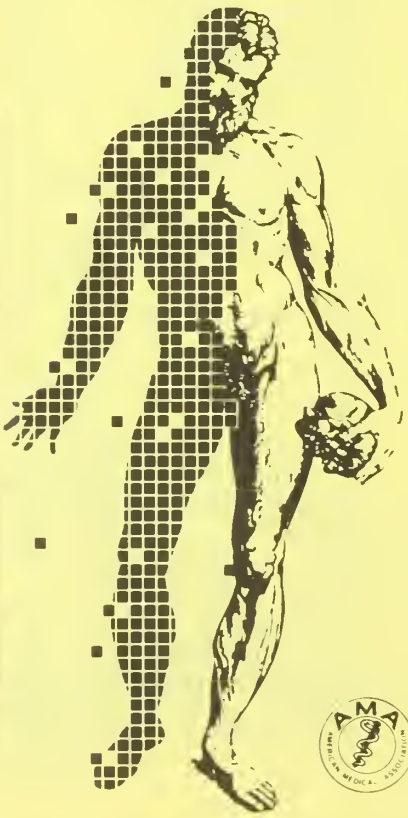

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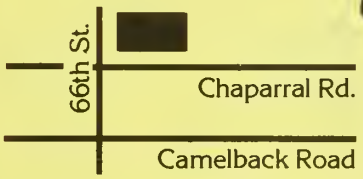

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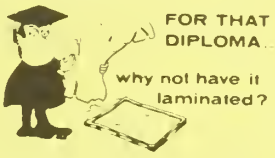

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Clinical Investigation

Pulmonary Disease at Autopsy in Patients With the Acquired Immunodeficiency Syndrome

JEANNE M. WALLACE, MD, *and* JAMES B. HANNAH, MD, *Los Angeles*

To characterize the postmortem pulmonary disease and analyze the effectiveness of antemortem diagnosis, we examined the clinical records and autopsy material from 54 patients who died of the acquired immunodeficiency syndrome. At autopsy, all patients had pulmonary disease. One or more specific diagnoses were made in 53, including opportunistic infection, nonopportunistic infection, and Kaposi's sarcoma. Multiple postmortem pulmonary diagnoses were established in 37. Respiratory failure was the most common cause of death.

Of the 97 pulmonary disorders discovered at autopsy, only 31 were diagnosed before death. The frequency with which infections were diagnosed during life varied according to the organism, and was significantly higher for Pneumocystis carinii *than for cytomegalovirus or bacterial agents. Pulmonary Kaposi's sarcoma was diagnosed in only 7% of patients with autopsy documentation. The yield of diagnostic procedures also varied according to the disease present. Sputum culture was relatively effective in detecting* Cryptococcus neoformans *and* Mycobacterium avium-intracellulare, *fiber-optic bronchoscopy was extremely useful for diagnosing* P carinii, *and one or more diagnoses were provided in 4 of 7 patients who underwent thoracotomy, but significant disease including cytomegalovirus infection and pulmonary Kaposi's sarcoma was frequently missed. Although the spectrum of lung disease found at autopsy is similar to that observed during life, the frequency of some pathologic processes including cytomegalovirus infection and Kaposi's sarcoma may be underrepresented in antemortem series.*

(Wallace JM, Hannah JB: Pulmonary disease at autopsy in patients with the acquired immunodeficiency syndrome. West J Med 1988 Aug; 149:167-171)

The acquired immunodeficiency syndrome (AIDS) is frequently complicated by pulmonary disease.[1] Since the initial experience with AIDS, various severe pulmonary disorders other than pneumonitis due to *Pneumocystis carinii* have been noted. Thus, the differential diagnosis in patients with AIDS and pulmonary disease has been extended to include not only AIDS-related opportunistic infections but also Kaposi's sarcoma involving the lung, a variety of nonopportunistic infections, and lymphoproliferative processes such as lymphoid interstitial pneumonitis and lymphoma.[1-5] The situation has been further complicated by the observation that several pathologic processes may occur in the lung simultaneously.

Although most cases of *Pneumocystis* pneumonia have been readily diagnosed during life, documenting other pulmonary disorders has been more difficult.[1-3,6-8] Thus, information regarding the frequency and types of pulmonary pathologic processes that affect patients with AIDS may be complete only at autopsy. To examine the spectrum, frequency, and ability to diagnose pulmonary disease in patients dying with AIDS, we reviewed the reports and slides of 54 autopsies done at UCLA Medical Center. For each case, the postmortem data were correlated with diagnostic information available in the antemortem clinical record.

Methods

We reviewed the autopsy records of all patients reported in the UCLA Medical Center Autopsy Registry to have died with AIDS. Of the 56 patients thus identified, 54 fulfilled the criteria for the diagnosis of AIDS established by the Centers for Disease Control[9] and were included in the study. For each patient, details of the gross description and the pathologist's formulation of the cause of death were recorded.

The available microscopic material from each case was reviewed. Histologic sections of lung, lymph nodes, spleen, adrenal glands, and other tissue indicated in the autopsy record to be of interest were examined. The specific diagnoses and pathologic findings noted in each type of tissue were recorded. The number of hematoxylin and eosin-stained slides reviewed varied from 2 to 13 (mean 4.5) for lung tissue and from 3 to 12 (mean 5) for extrapulmonary tissue. In 45 cases, 1 or more Ziehl-Neelsen-stained slides from the lung and extrapulmonary sites were studied. In 48 cases, at least one lung section stained with Gomori's methenamine-silver nitrate solution was examined. Lung sections stained with Gram's stain in 22 cases and with periodic acid-Schiff stain in 19 cases were evaluated. Additional slides from the available tissue blocks were prepared when necessary.

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Presented in part at the annual meeting of the American Thoracic Society, May 1985, Anaheim, California.
Reprint requests to Jeanne M. Wallace, MD, Department of Medicine, LAC-Olive View Medical Center, 14445 Olive View Dr, Sylmar, CA 91342-1495.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus

The results of cultures taken during the autopsies were compiled from records available in the UCLA Clinical Microbiology Laboratory. All but ten of the autopsies were done within 24 hours of death. Tissue for postmortem cultures was not taken in seven cases for which the time of autopsy was delayed. Lung tissue was cultured for mycobacteria in 47 cases (on Lowenstein-Jensen and Wallenstein plates and in Middlebrook 7H12 agar), aerobic bacteria in 40 cases (on blood, chocolate, and MacConkey's agar), fungi in 28 cases (in Sabouraud's agar and on inhibitory mold and liver infusion agar), and viruses in 45 cases (in human embryonic lung fibroblast, human foreskin fibroblast, and primary African green monkey cell lines).

To obtain a data base that would allow correlation of details of the antemortem diagnostic evaluation with the autopsy findings, the clinical record of each patient was reviewed. Of the 54 patients included in the study, 36 had been treated at UCLA Medical Center and 18 at a Southern California Kaiser Permanente facility.* Autopsy data were correlated with antemortem data to determine the frequency with which the pulmonary diagnoses made at autopsy was established during life and the diagnostic yield of pulmonary procedures carried out during the four weeks before death. The pulmonary diagnostic procedures included sputum collection, diagnostic thoracentesis, fiber-optic bronchoscopy, and diagnostic thoracotomy. During fiber-optic bronchoscopy, specimens of bronchial washings, brushings, and fluoroscopically guided transbronchial biopsies were obtained. Bronchoalveolar lavage was done during 12 fiber-optic bronchoscopies. Pulmonary specimens obtained antemortem were processed in the same manner as the autopsy specimens except, in addition, sputum and bronchoscopy smear or sediment preparations were fixed in a 95% ethanol solution and stained by the Papanicolaou technique; and sputum, bronchoscopy, and thoracotomy specimens were submitted for *Legionella* direct antibody fluorescent staining and cultured by the method of Edelstein.[10]

Results

Patient Population Studied

The study group consisted of 53 men and 1 woman. All 54 patients had at least 1 identifiable risk factor for the development of AIDS: 51 had a history of a homosexual life-style, 6 were illicit intravenous drug users, 3 had received blood transfusions within five years before the time that AIDS was diagnosed, 1 was a recent immigrant from Haiti, and 1 had a history of heterosexual contact with an intravenous drug abuser. The diagnosis of AIDS was based on the documentation of opportunistic infection in 25 patients, Kaposi's sarcoma in 2, and both opportunistic infection and Kaposi's sarcoma in 27. The age at the time of death ranged from 23 to 72 years (mean 38 years). The mean interval from the time AIDS was diagnosed to the time of death was 7.2 months (range less than 1 to 29 months).

Autopsy Findings

The cause of death determined at autopsy for each of the patients studied is shown in Table 1. Respiratory failure was the most frequent cause of death. Severe widespread pulmonary parenchymal disease associated with pulmonary infection, Kaposi's sarcoma, or both, occurred in all 41 patients in whom respiratory failure was considered a major cause of death. The cause of death was considered to be overwhelming sepsis or widespread Kaposi's sarcoma in nine patients and central nervous system disease in three. Substantial pulmonary disease was also noted in all but one of these cases. In one patient, the cause of death could not be determined from the findings at autopsy. The only pulmonary disease found in this patient was a small focus of Kaposi's sarcoma.

The intrathoracic pathologic processes found at autopsy are summarized in Table 2. All 54 patients had some form of pulmonary parenchymal disease. Diffuse alveolar damage[11] was observed in 35 patients (65%). The exudative phase of diffuse alveolar damage, characterized by interstitial edema and hyaline membranes, was noted in three patients. The proliferative phase, with regeneration of alveolar epithelium, interstitial inflammation, and fibrosis, was present in 18. In 14 patients, both exudative and proliferative phases were

TABLE 1.—*Cause of Death Determined at Autopsy in 54 Patients With the Acquired Immunodeficiency Syndrome*

Cause of Death	*Number of Patients*
Respiratory failure	31
Respiratory failure and sepsis	10
Sepsis	7
Central nervous system process	3
Overwhelming Kaposi's sarcoma	1
Overwhelming Kaposi's sarcoma and sepsis	1
Unable to determine	1

TABLE 2.—*Intrathoracic Disease Found at Autopsy in 54 Patients With the Acquired Immunodeficiency Syndrome*

	Patients	
Pathologic Process	*No.*	*%*
Pulmonary parenchymal	*54*	*100*
Diffuse alveolar damage	35	65
Bronchopneumonia	18	33
Kaposi's sarcoma	14	26
Focal interstitial inflammation	13	24
Hemorrhage	12	22
Pulmonary edema	6	11
Airway	*31*	*57*
Tracheobronchitis	25	46
Kaposi's sarcoma	4	7
Bronchiolitis obliterans	2	4
Bronchiectasis	2	4
Pulmonary vascular	*12*	*22*
Thromboembolic disease	11	20
Medial thickening or intimal proliferation	1	2
Lymphadenopathy	*28*	*52*
Kaposi's sarcoma	16	30
Infectious agent	5	9
Lymphoma	1	2
Pleural	*43*	*80*
Effusions	35	65
Adhesions	8	15
Kaposi's sarcoma (direct involvement)	3	6
Empyema	3	6

*1. Jeffry Strumpf, MD, assisted in obtaining clinical information on the patients treated in the Southern California Kaiser Permanente system.

represented in different areas of the lung sections. All 35 patients with diffuse alveolar damage had autopsy evidence of at least one pulmonary infection: cytomegalovirus (CMV) in 22 (63%), *P carinii* in 20 (57%), *Cryptococcus neoformans* in 5 (14%), *Mycobacterium avium-intracellulare* in 5 (14%), pyogenic bacteria in 2 (6%), and adenovirus in 1 (3%). Mechanical ventilation was used during the month before death in 18 (51%).

Among the 18 patients with early to extensive bronchopneumonia noted at autopsy, 6 had corresponding radiographic abnormalities before death. In 14 (26%) patients, pulmonary lesions of Kaposi's sarcoma similar to those of previous descriptions were noted.[3-5,8] Focal interstitial pneumonitis (focal mononuclear cell inflammation with or without interstitial fibrosis and no reactive pneumocytes) was found in 13 patients (24%). Of 12 (22%) patients with gross evidence of pulmonary hemorrhage, 4 had pulmonary Kaposi's sarcoma and 5 had thrombocytopenia—platelet count less than 100,000 per μl—documented during the month before death.

Tracheobronchitis, the most common airway abnormality, was nonspecific in all but one patient with ulcerative lesions due to CMV infection and one with the typical plaques of *Candida albicans* infection. Tracheobronchial involvement with Kaposi's sarcoma was observed in four patients and caused significant large airway obstruction in two. In two cases, bronchiolitis obliterans was associated with diffuse alveolar damage. In one of two patients with severe bronchiectasis, there was evidence of airway colonization without invasion by *Aspergillus fumigatus.*

Pulmonary vascular disease was not prevalent in this series, evidence of recent thromboembolic disease involving only small distal vessels in all but two patients being the most common finding.

Englargement of the mediastinal or hilar lymph nodes (or both), noted in half the patients studied, was most frequently due to invasion with Kaposi's sarcoma. In six patients, a specific cause for the lymphadenopathy was not found.

Pleural effusions were found in 35 patients (65%) and were bilateral in each case. The effusions were substantial—greater than 500 ml—in 16 patients. Of these, 13 had Kaposi's sarcoma involving the mediastinum or pleural surface (or both), 1 had mediastinal lymph node involvement with *C neoformans,* 1 had contiguous gram-negative bacillary pneumonia, and 1 had no specific cause found. The appearance of the pleural fluid—serous versus serosangineous—did not correlate with the cause of the effusion. Empyema, present in three patients, was associated with a chest tube in two and bacterial pneumonia in one.

Correlation of Autopsy and Antemortem Findings

Table 3 shows the pulmonary diagnoses made antemortem and postmortem and the frequency with which each of the postmortem diagnoses was missed during life. At least one specific pulmonary diagnosis was made at autopsy in all but one patient. Only 31 (32%) of the 97 postmortem diagnoses were made before death. In 53 patients who had one or more specific pulmonary autopsy diagnoses, all diagnoses were made antemortem in 16 (30%) and none were made antemortem in 21 (40%). In 16 patients (30%), at least one autopsy diagnosis was established correctly before death, but one or more coexisting process were not discovered until the autopsy was done.

The pulmonary disorders detected most frequently antemortem were *P carinii* and *C neoformans* pneumonia. None of the patients with *Pneumocystis* or cryptococcal pneumonia in whom the diagnosis had been missed antemortem had undergone a pulmonary diagnostic procedure in the month before death. Most of the cases of pneumonitis due to a specific bacterial agent or CMV and pulmonary Kaposi's sarcoma were missed during life. Yet, each was a common postmortem diagnosis. At autopsy, CMV pneumonitis, documented in 31 patients (57%), was encountered more frequently than *P carinii* infection. The frequency of intrathoracic Kaposi's sarcoma was greatly underrepresented during life. Of the 29 patients in this series with Kaposi's sarcoma, intrathoracic involvement was documented in 21 (72%). Within the thorax, the sarcoma involved lung parenchyma in 14 patients, mediastinal or hilar lymph nodes (or both) in 16, and the pleural surface in 3. In one patient, the mediastinum was the only demonstrable site of Kaposi's sarcoma. The eight patients with no intrathoracic involvement had relatively limited disease confined to the skin in seven, and to the skin and gastrointestinal tract in one.

The diagnostic yield of all pulmonary procedures carried out within a month before death is shown in Table 4. Sputum cultures were useful for documenting pulmonary infection due to *C neoformans* and *M avium-intracellulare* and for identifying pathogenic bacteria. Of the 43 fiber-optic bronchoscopies done, 19 (44%) provided at least one pulmonary diagnosis. Fiber-optic bronchoscopy was most useful for documenting the presence of *P carinii* pneumonia. Only 3 of 20 (15%) fiber-optic bronchoscopies done in patients with CMV pneumonitis provided specimens with diagnostic cytopathic changes. In no case was Kaposi's sarcoma or the organism responsible for bacterial pneumonia found by bronchoscopy. Diagnostic thoracotomies performed during the month before death provided at least one specific diagnosis in four of seven patients (57%), but in each case at least one diagnosis was missed. Diagnostic thoracotomy documented the presence of Kaposi's sarcoma in only one of three cases (33%) and CMV pneumonitis in only one of seven (14%).

Discussion

Although patients with AIDS frequently undergo pulmonary diagnostic procedures,[1,2,6,7] the results may be incomplete because of the complex nature of the disease and the

TABLE 3.—*Pulmonary Diagnoses Made Antemortem and Postmortem in 54 Patients With the Acquired Immunodeficiency Syndrome*

Diagnosis	Patients, No.*		
	Antemortem Diagnosis	Postmortem Diagnosis	Diagnoses Missed Antemortem, %
Pneumocystis carinii	15	21	29
Cryptococcus neoformans	4	7	43
Mycobacterium avium-intracellulare	5	11	54
Bacterial pneumonia	2	12	83
Cytomegalovirus†	4	31	87
Kaposi's sarcoma	1	14	93
Herpes simplex virus	1	1	0
Adenovirus	0	1	100

*Some patients had more than one diagnosis.
†Includes only patients in whom cytomegalovirus inclusion bodies were found in pulmonary specimens.

limited size of the specimens. In this study, information available at autopsy was correlated with the results of antemortem diagnostic evaluations. The objectives were to better define the types and frequency of pulmonary disorders in patients with AIDS and to provide a clearer perspective of the currently available diagnostic capabilities. The findings indicate that many patients dying with AIDS have significant pulmonary disease that has been undiagnosed during life.

All of the patients in this series had some form of pulmonary disease, and all but one had at least one specific pulmonary diagnosis made during the postmortem examination. The most frequent cause of death was respiratory failure. These findings emphasize the high frequency and important role of pulmonary complications in the morbidity and mortality of AIDS. The spectrum of pulmonary disease found at autopsy in this series was the same as that reported previously in antemortem studies.[1,2] The striking finding in our study was that most patients had more than one coexisting pathologic process, most of which were unrecognized during life.

Missed antemortem diagnoses were most frequently those of CMV pneumonitis, bacterial pneumonia, or pulmonary Kaposi's sarcoma. More than half of our patients had cytopathic changes in pulmonary autopsy tissue consistent with CMV infection. The frequency with which CMV pneumonitis has been reported in AIDS patients has been considerably greater in autopsy series[3-5] than in antemortem studies,[1,6,7] reflecting the difficulty of diagnosis during life. In our series, only four patients had cytopathic evidence of CMV pneumonitis observed in pulmonary specimens taken during life, although it was found at autopsy in 31. By contrast, *Pneumocystis* pneumonitis was very effectively diagnosed by fiber-optic bronchoscopy during life. The only patients in whom *P carinii* was missed were those who did not undergo an appropriate evaluation. Other opportunistic pulmonary infections frequently detected during life included those due to *C neoformans* and *M avium-intracellulare.* Sputum collection or bronchoscopy appeared to be a relatively sensitive means of detecting these infections.

The occurrence of common pyogenic bacterial pneumonia in patients with AIDS is now well recognized.[12] Although bacterial pneumonia may have developed as an immediate preterminal event in some of our patients, consistent radiographic findings were documented before death in six. Identifying the responsible bacterial agent before death was difficult, the organism being correctly defined by the sputum culture in only two patients and by fiber-optic bronchoscopy or diagnostic thoracotomy in none.

Intrathoracic Kaposi's sarcoma, a common finding among patients with this malignant disorder, was also greatly underdiagnosed during life. The most frequent intrathoracic sites were the mediastinum and the lung parenchyma. Kaposi's sarcoma was the most common cause of mediastinal lymphadenopathy in this series. All but 3 of our 16 patients with notable pleural effusions had Kaposi's sarcoma, of whom only 2 had direct pleural involvement and 12 had extensive mediastinal involvement. Lymphatic obstruction from mediastinal tumor retards absorption of pleural fluid and is a well-recognized cause of pleural effusion.[13] According to the experience reported here, Kaposi's sarcoma involving the mediastinum is an important cause of pleural effusion in patients with AIDS.

Documenting pulmonary Kaposi's sarcoma during life may be difficult.[3,8] In our series, it was diagnosed antemortem in only 1 of 14 patients. Although the diagnosis has been established by transbronchial biopsy,[14] most reports emphasize the necessity of obtaining larger specimens by thoracotomy.[1,8] Even an open approach can fail to provide the diagnosis. In this study, pulmonary Kaposi's sarcoma was detected in only one of three patients who underwent diagnostic thoracotomy. The presence of skin lesions is an important diagnostic clue indicating that pulmonary disease may be due to Kaposi's sarcoma. All but one of our patients with intrathoracic involvement had skin manifestations.

In addition to the specific diagnoses discussed here, many of the patients in this series had nonspecific pathologic processes that contributed to the development of respiratory failure. Diffuse alveolar damage was noted in 35 patients. The histologic findings of this disorder represent a nonspecific reaction to a variety of insults that cause alveolar epithelial and endothelial cell injury.[11] Pulmonary infection was present in all of our patients who had diffuse alveolar damage. Mechanical ventilation with high concentrations of oxygen or sepsis or both are additional factors that may have contributed to the development of diffuse alveolar damage in some of our patients. Pulmonary hemorrhage, another nonspecific pulmonary complication observed by autopsy, occurred in 12 patients, 4 with pulmonary Kaposi's sarcoma and the rest with various infections. Previous reports[3-5,8] have documented the occurrence of pulmonary hemorrhage in patients with Kaposi's sarcoma. Five of our patients with thrombocytopenia were predisposed to intra-alveolar

TABLE 4.—*Diagnostic Yield of Pulmonary Procedures in 54 Patients With the Acquired Immunodeficiency Syndrome*

	Procedures, No. Diagnostic/No. Performed (%)*					
Diagnosis	*Sputum Collection*		*Fiber-optic Bronchoscopy*		*Diagnostic Thoracotomy*	
Pneumocystis carinii	ND		14/14	(100)	2/2	(100)
Cytomegalovirus†	0/14	(0)	3/20	(15)	1/7	(14)
Cryptococcus neoformans‡	3/4	(75)	1/1	(100)		ND
Mycobacterium avium-intracellulare‡	4/6	(67)	3/5	(60)	1/3	(33)
Bacterial‡	2/5	(40)	0/5	(0)	0/2	(0)
Kaposi's sarcoma	ND		0/8	(0)	1/3	(33)

ND=not done

*All procedures were carried out within 4 weeks before death.
†Only specimens showing cytomegalovirus inclusion bodies were considered diagnostic.
‡Specimens showing the organism microscopically, in culture, or both were considered diagnostic.

bleeding as a complication of pulmonary infection. The possibility of pulmonary hemorrhage should be considered in patients with AIDS who experience rapid respiratory deterioration. Although 11 of our patients (20%) had evidence of recent pulmonary emboli, only small distal vessels were involved in all but two. Thus, it is unlikely that thromboembolic disease contributed significantly to morbidity or mortality in most of our patients.

In conclusion, we emphasize that pulmonary disease in the patient with AIDS often is not completely characterized by one or even two diagnoses. Coexisting infection particularly due to CMV, Kaposi's sarcoma, or nonspecific pathologic processes such as diffuse alveolar damage or pulmonary hemorrhage may complicate what would superficially appear to be a clearly defined disorder. In some cases, the complete pulmonary diagnosis may require invasive procedures or an extended period of time for identifying a pathogenic organism. Therefore, a diagnostic strategy aimed at defining the pulmonary disease as thoroughly as possible must be planned early in the evaluation. As newer and possibly more effective treatment modalities for the various pulmonary complications of AIDS become available, refinement of the diagnostic process will become increasingly important.

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Book Review

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

Management of Spinal Cord Injuries

Edited by Ralph F. Bloch, MD, PhD, FRCP(C), Associate Professor of Medicine, McMaster University Faculty of Health Sciences, and Director of Neurotrauma Program, Chedoke Rehabilitation Centre, and Mel Basbaum, MSW, Social Work Department, Chedoke-McMaster Hospital, Chedoke Rehabilitation Centre, Hamilton, Ontario, Canada. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1986. 447 pages, $53.50.

The reluctance with which I embarked on fulfilling my commitment to writing a review of this book changed to delight as soon as I encountered the crisp clarity and insight in its pages.

"Injuries to the spinal cord are among the most devastating physical insults an individual may suffer. They spare the mind, leaving intact all desires and aspirations, while rendering the body unable to obey many, if not most, of the commands necessary to achieve these goals.

"Of course tragedy still holds center stage in many cases. But with ideal management combined with the buoyant will of most human beings, many patients with spinal cord injuries bounce back with a vigor that never fails to thrill me."

A frank appraisal of controversies in neurosurgical and orthopedic management sets the pace for a critical review of the literature, combined with the opinions and experience of a multidisciplinary team of authors from Canada, England, and the US. The chapters on pain, autonomic dysfunction, respiratory pathophysiology, gastrointestinal complications, urinary tract infections, sexual function, and resocialization deserve particular praise for their concise, candid styles and thoroughness. Each chapter resembles an epitome of progress in spinal cord injury management.

The book is an excellent resource for physicians and allied health professionals who treat paraplegics and quadriplegics on a regular or even an occasional basis. It highlights the medical, technologic, and attitudinal advances through which tragedy often gives way to brilliant successes. In the words of Dr Frank Krusen, one of the fathers of rehabilitation medicine, "Now that we have added years to life, let us add life to years."

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Clinical Investigation

Rock-Climbing Injuries in Yosemite National Park

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This study was presented in part at the annual meeting of the Wilderness Medical Society at Aspen, Colorado, in August 1986 and at "Mountain Medicine 1987," Leavenworth, Washington, in November 1987.

We questioned 220 injured rock climbers or their partners seen consecutively at the Yosemite (California) Medical Clinic over 3½ years regarding details of their accidents. Injury type and location were extracted from medical records and severity quantified. The National Park Service rescued 27% of the climbers. Injured climbers were characteristically male (88%) and experienced (mean 5.9 years) and typically fell while leading climbs (66%). Among 451 injuries, 50% were to the skin or subcutaneous tissues, while 28% involved the lower extremity and were predominantly fractures. In terms of each climber's most severe injury (n = 220), 45% involved the lower extremities (30% from the ankle alone). Head injury or hypothermia caused 12 of 13 fatalities, showing the lowest case-fatality rate reported to date among injured climbers (6%). Rescue personnel successfully managed airways in victims of head injuries, anticipated and treated complications of hypothermia, and stabilized fractures. Victims requiring immediate extensive surgical intervention or blood transfusion usually died before rescue could be effected.

(Bowie WS, Hunt TK, Allen HA Jr: Rock-climbing injuries in Yosemite National Park. West J Med 1988 Aug; 149:172-177)

Many studies of climbing injuries have been carried out around the world but none in what has been called "the climbers' Mecca"—Yosemite National Park, California. In 1953 Ferris estimated that there were 18,722 "man-mountain days" for the entire United States.[1] By 1987 Yosemite alone hosted an estimated 25,000 to 50,000 climber-days (John Dill, Yosemite Search and Rescue, US National Park Service, oral communication, July 1987). As the participation in this sport has increased, so has the number of injuries.[2]

Most mountaineering medical literature has stressed severe injuries, snow-related accidents, and high-altitude physiology.[2-7] For example, Foray and co-workers, in an analysis of 1,819 mountain-climbing accidents in the Chamonix-Mont-Blanc region, found 69% of all cases classifiable as "trauma"; 22% as "exposure to cold"; and the rest as "mountain sickness, severe fatigue, and accidents due to thunderbolts."[7] Climbers on Mount McKinley (Alaska) in 1976 commonly suffered acute mountain sickness or frostbite in addition to fractures.[5] In the Grand Tetons (Wyoming), much morbidity and most climber mortality were attributed to travel on snow,[2] while most injured climbers studied in the eastern Sierra Nevada (California) had acute mountain sickness or hypothermia in addition to trauma.[6] No one has described injury patterns in a relatively low-altitude, snow-free area such as Yosemite, where nearly all climbing occurs on rock.

Injury rates have been estimated in other regions, where climber registration is required.[2,5] Climbers are not required to register in Yosemite, and injury rates there cannot be determined. A different measure, the "case-fatality rate"—the percent of fatalities among all injured climbers—has been useful, therefore, by giving information about the lethality of injury. Many studies of climbing injuries have yielded high case-fatality rates—as high as 41%.[1,2,5,7] These studies, however, used data extracted from rescue or anecdotal reporting only, not data collected at local medical facilities where minor injuries of self-rescued climbers are often treated. Injuries may appear inappropriately severe because of this selection bias, leading to a distorted perception of climbing risks.

Yosemite National Park offers a unique environment where minor injuries can be documented as completely as severe injuries. The park is a remote area served by a single medical clinic that also acts as the medical base station for all rescues.

Another measure of injury, the Injury Severity Score (ISS),[8] has been used to assess injury severities among climbers.[2] No one has yet evaluated the usefulness of adapting the ISS to the study of climbing injuries.

This descriptive study was initiated to define the mechanism, pattern, and severity of rock-climbing injuries in Yosemite; to evaluate the care of those injuries; and to identify strategies for reducing the number of injuries where suggested by particular injury patterns. It was hypothesized that without the mountaineering hazards of high altitude, cold, avalanches, and long slides on snow, the spectrum of injuries in Yosemite would be different from that previously reported

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ABBREVIATIONS USED IN TEXT
AIS = Abbreviated Injury Scale
ISS = Injury Severity Score

in the literature from other climbing areas. This study did not attempt to determine the rate of injury in Yosemite.

Background Terminology

A "climber" was defined as anyone familiar with climbing techniques, nomenclature, and rating systems standard in the United States. Deliberately excluded were injuries involving "scramblers," persons climbing rocks despite an unfamiliarity with rating systems or the use of ropes.

"Climbing injuries" include those injuries suffered by climbers during approach or execution of or descent from a climb. Customarily, a "lead" climber, attached to a rope, begins climbing as the "following" climber plays out the rope. The leader places devices in the rock—"protection"—through which the rope can slide and support the climber if he or she falls. Once in a safe position, the leader anchors to rock and takes up rope as the follower climbs. "Free climbing" implies the use of only the climber's body and extremities, relying on "protection" only in the event of a fall, whereas "aid climbing" uses the "protection" for support as well as safety on steeper, longer climbs. "Bouldering" denotes unroped practice climbing, usually within 5 m (15 ft) of the ground. A "rappel" is a descent by sliding down a rope, usually using a metal device. For further explanation of climbing terminology, readers are referred to Royal Robbin's *Basic Rockcraft*.[9] Among fifth-class climbs—climbs generally requiring a safety rope—difficulty is denoted in Yosemite using a decimal scale of roughly equivalent increments, designated 5.1 to 5.13.

Patients and Methods

Beginning in April 1984, data were collected using questionnaires completed by all injured climbers or their partners who were seen at the Yosemite Medical Clinic or rescued by the US National Park Service's Search and Rescue team. No one refused to complete the questionnaire.

Questionnaires solicited standard demographic data; previous climbing experience; the route and difficulty of the climb; and details of the accident, including cause, length of fall, and mechanism of injury. Drug or alcohol use was recorded, when reported. Yosemite Search and Rescue records were reviewed to determine the medical interventions used by park rescuers.

Injury data were extracted from clinical records or autopsy reports and coded according to anatomic regions. Injury "type" was classified as "fracture," "sprain," or "laceration," for example. The severity of each injury was quantified using the Abbreviated Injury Scale (AIS)[10] on a scale of 1 to 5 reflecting threat to life: minor to virtually unsurvivable. Overall injury severity of multiple injuries was calculated using the Injury Severity Score (scale 0 to 75), which is mathematically derived by adding the squares of the highest AIS code for each of the three most severely injured body regions.[8] Injury "site" and "type" were analyzed for all injuries suffered by all climbers and for the subset of "single most severe injuries" suffered by each climber.

Some climbers severely injured in remote regions of the park were rescued by the Park Service and flown by helicopter directly to definitive hospitals outside the park. The Yosemite clinic monitored all such evacuations, and data were collected from the medical records of those hospitals. Any injured climbers who rescued themselves and received medical care at home or elsewhere could not be detected by this study. These "drive-aways" were felt to be few and to have minor injuries because the remote location of Yosemite made it difficult for them to seek care elsewhere.

Data were analyzed using the "Excel" and "Statview 512+" data-base and statistical software programs. For hypothesis testing we used χ^2 analysis, unpaired Student's t test, and, where applicable, the Mann-Whitney equivalent of the Student's t test or the Spearman's rank correlation coefficient for nonparametric data (the Injury Severity Score, for example, does not follow a normal distribution in this population; thus, the Student's t test is invalid for this variable).

Results

In 3½ climbing seasons, 220 injured climbers were treated for 451 injuries for an average of 2 injuries per victim; 27% were rescued by the Park Service, the rest being first seen at the Yosemite Medical Clinic. Thirteen climbers died (case-fatality ratio 6%).

Of the injured climbers, 88% were male, and the mean age was 27.5 years (range, 14 to 64 years). The mean number of years of climbing experience was 5.9 years (men 6.2, women 3.6, $P < .005$). The injured climbers had climbed an average of 11 days in the 30 days preceding their injury. About 31% reported a previous climbing injury more severe than minor abrasions, of which 60% were to the lower extremities. Most victims (63%) were from California; 19% were foreign, representing 14 nations. A total of 71% reported being able to lead climbs of 5.10 or harder. During the 30-day period before injury, most climbers were climbing at or near their maximal ability (correlation coefficient = .91). Only a minority of falls (14%) occurred when victims were attempting climbs rated beyond their most recent standard (correlation coefficient = .74). Six reported using helmets on the day of injury. One reported using drugs or alcohol immediately before injury.

More injuries occurred in the spring (47%) than in summer or autumn (21% and 26%, respectively). Injuries were disproportionately higher on weekends (43% on Saturdays and Sundays alone) than on weekdays (57% over the five days) ($P < .0001$). Time of injury was distributed evenly about a peak at noon, although the number of "severe"—ISS > 12[11]—injuries was disproportionately increased after 5 PM (35%, $P < .02$). No area of Yosemite was represented disproportionately, except for the Cathedral Rocks area, where severe injuries were more frequent ($P < .001$). The average clinic medical expense for climbers was $233, while rescued climbers averaged clinic expenses of $360. Nearly all (89%) climbers paid their clinic bills in full.

Mechanism of Injury

Falls suffered by the lead climber were responsible for the majority of injuries (66%, $P < .05$) (Table 1). Length of falls ranged from 0.6 to 244 m (2 to 800 ft; mean 13 m [43 ft], median 8 m [25 ft]). On 29% of leader falls, "protection" pulled out of the rock during a fall, resulting in a longer fall (mean fall length 17 m [55 ft]; $P = .05$). Only 12% of injuries occurred while "aid" climbing. Six climbers were injured (one fatally) while climbing without a rope, and seven were

TABLE 1.—*Immediate Event Leading to Injury*

Event	Injury No.	Injury %
Leader fall	144	65
Bouldering fall	14	6
Rock fall	13	6
Illness	12	6
Exposure	11	5
Follower fall	4	2
Anchor failure	3	1
Rappel	2	1
Other	17	8
	220	100

TABLE 2.—*Injuries by Body Region*

Body Region	All Injuries No.	All Injuries %	Single Most Severe Injury No.	Single Most Severe Injury %
Skin/subcutaneous	227	50	65	30
Lower extremity				
Femur	7	2	5	2
Knee	10	2	8	4
Tibia/fibula	15	3	9	4
Ankle	81	18	66	30
Foot	14	3	10	5
	127	28	98	45
Upper extremity				
Shoulder	4	1	2	1
Forearm	6	1	3	1
Wrist	8	2	4	2
Hand	11	3	8	4
	29	6	17	8
Skull/brain	25	6	14	6
Thorax				
Chest	5	1	3	1
Thoracic spine	6	1	4	2
	11	2	7	3
Face/neck	10	2	3	1
Abdomen	6	1	2	1
Bony pelvis	4	1	2	1
Hypothermia	12	3	11	5
Unknown	...	...	1	0
	451	100	220	100

TABLE 3.—*Types of Climbing Injuries at Yosemite National Park*

Type	All Injuries No.	All Injuries %	Single Most Severe Injury No.	Single Most Severe Injury %
Fracture	130	29	85	39
Abrasion	111	25	21	10
Contusion	66	15	19	9
Laceration	64	14	32	14
Sprain/strain	47	10	35	16
Hypothermia	12	3	11	5
Dislocation	9	2	8	4
Closed space hemorrhage	6	1	4	2
Concussion	5	1	3	1
Other	1	0	1	0
Unknown	...	...	1	0
	451	100	220	100

injured while descending without a rope. Rappelling contributed only 1% of all injuries. There was one case of equipment failure when a protection bolt drilled previously into the rock pulled out under the force of a fall.

Four following climbers were injured. Followers are usually considered to be in a safe position while climbing because the climber above pulls up the rope as the follower ascends, preventing all but short falls. In two of the accidents, the followers were traversing sideways when they fell, causing a pendulum-like fall to occur, of greater distance and force than most follower falls. One fatality occurred when a follower was hit by a huge boulder dislodged by his lead climber's fall. The final follower accident resulted from inadequate belay from above.

Most injuries occurred on rock ledges or rock face (47%), while falls to the ground and falling rock caused 27% and 10% of injuries, respectively. Weather was a factor in 23 cases, 3 fatal (hypothermia). The most unusual sources of injury included a bat bite and an episode of assault by another climber with a piton hammer.

Pattern of Injury

Climbers' injuries are shown by body region in Table 2. Among all 451 injuries, regardless of severity, most (50%) were to the skin or subcutaneous tissues. After excluding these injuries, which were almost always minor, 57% of the remaining 224 injuries were to the lower extremities. Among all injury types, predominantly external injuries (lacerations, contusions, and abrasions) were the most common (together 53%), then fractures (29%), and sprains (10%) (Table 3). Most (63%) fractures were to the lower extremity (primarily to ankle, tibia or fibula, and foot). The site and type of skeletal injuries are depicted in Figure 1.

The injury site and type were also analyzed by each climber's single most severe injury (n = 220) because most climbers presented with one severe injury and one associated minor complaint, typically abrasions. Ankle injuries alone—mostly fractures—made up 30% of climbers' single most severe injuries, making the ankle the most commonly injured body region causing climbers to seek medical attention. More than 44% of climbers presented with complaints relating to some part of the lower extremity. Only 6% of single most severe injuries were attributed to head trauma, but 9 of these 14 were fatal. More than a fourth of climbers presented with only skin or subcutaneous tissue injuries, nearly always of minor severity.

Injury Severity

Injury severity scores are depicted in Figure 2. Eleven hypothermia cases could not be coded because hypothermia is not included among diagnoses in the Abbreviated Injury Scale. Notably, the vast majority of injuries were minor. The median ISS was 4.0 (mean 6.1). The group of cases rescued by Search and Rescue teams had a median ISS of 9, while the median for cases first presenting to the clinic was 4 ($P < .05$). The median ISS was 4 for both male and female subgroups. "Minor" injuries (ISS less than 5)[11] made up 59%, "moderate" (ISS from 5 to 12) were 36%, and "severe" (13 to 75) were 5%. The ISS was greater for lead climbers (median 4) than for followers (median 1, $P < .01$).

The ISS was positively correlated with the length of fall ($r = .86$) (Figure 3). Correlation was poor ($r = .42$), however, when the two longest falls were excluded (both 243 m [800

ft], ISS 75). For severe injuries—an ISS of greater than 12—the relationship between the length of fall and injury severity was stronger ($r = .91$ without the two outlying cases). Most falling lead climbers were stopped by their ropes and safety systems (63%), attenuating the impact.

Time to Medical Care

The median time of arrival by park medics was 1.5 hours after injury (range, 10 minutes to 36.5 hours). After a Search and Rescue team arrived, the median time for stabilization and transport to clinic, where applicable, was 1.6 hours (range, 1 to 38.5 hours). Victims transported to tertiary care centers arrived a median of 7.25 hours after injury (range, 2 to 38.5 hours). Self-rescued climbers presented to the clinic after a median of 4.25 hours (range, 15 minutes to 2 weeks).

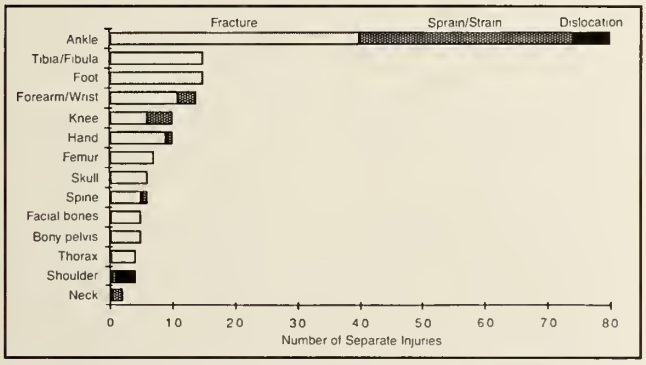

Figure 1.—The graphs show the site and type of skeletal or joint injuries (n = 183).

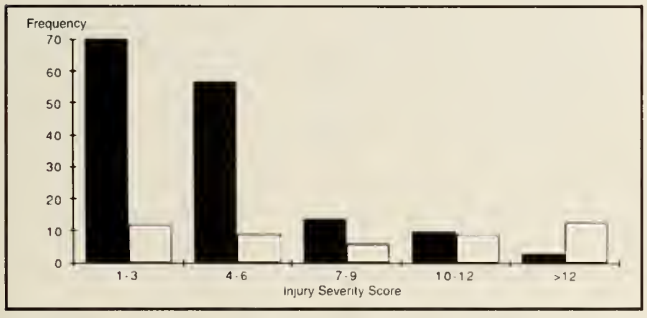

Figure 2.—The graphs show the different frequencies of Injury Severity Scores (scale of 1 to 75) between self-rescued climbers **(solid bars)** and climbers rescued by the Yosemite National Park Service **(empty bars)** ($P < .05$).

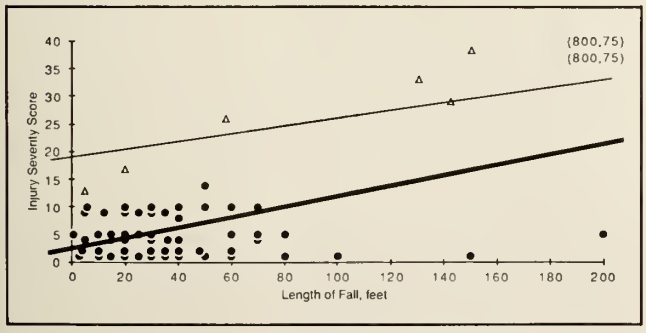

Figure 3.—The graphs show climbing injury severity scores (ISSs) at various fall lengths (mean 42.8 ft, median 25 ft). Two fatalities, both 800-ft falls with ISS 75, are not shown because of scale. △ = severe injuries ($r = .975$ [$r = .914$ if 800-ft falls are excluded]), ● = all injuries ($r = .858$ [$r = .419$ if 800-ft falls are excluded])

Severe Injury Cases

Of the 220 injured climbers, 20 were considered severely injured (ISS > 12), and 13 of these died. The seven survivors had injury severity scores ranging from 13 to 22. Fatally injured climbers had scores from 26 to 75. Injuries among the survivors included two cerebral contusions, a Le Fort I (horizontal maxillary) fracture, three wrist fractures (one crushed), multiple lacerations, an open skull fracture, an open digital fracture, a femoral neck fracture, a case of multiple pelvic fractures, a bladder contusion, an open trochanteric fracture, a case of three rib fractures, a dislocated ankle, and multiple contusions and abrasions ranging from mild to severe. Severely injured climbers had disproportionately fewer lower extremity injuries than mildly or moderately injured climbers ($P < .0001$). Severe injury was associated with occurrence after 5 PM ($P < .02$), with inclement weather ($P < .05$), with climbing further above the ground (mean pitch at injury = ninth versus third pitch for climbers not severely injured; ($P < .001$), and with longer fall (mean 62 m [203 ft], $P < .0001$). Severe injury was also more frequent in the Cathedral Rocks area ($P < .001$).

Medical Intervention

Medical intervention by rescue personnel was difficult and often delayed by technical rescue problems. In general, Park Service medics stabilized injured climbers using mask or nasal oxygen, oral or esophageal obturator airways, administering isotonic crystalloid solutions, or applying cervical collars, backboards or Kendrick extrication devices, and air splints. These interventions slowed, but did not preclude, rescue by litter lowering, carrying out, or air evacuation. At the clinic, airway patency and respiratory and circulatory sufficiency were established and associated injuries investigated. One injured climber required intubation, but no tube thoracostomies were needed. Two climbers with tachycardia, diaphoresis, and peripheral vasoconstriction responded promptly to the intravenous administration of Ringer's lactated solution. If blood transfusions had been needed, the clinic would have requested units to be flown to the park with an air transport team. Appropriate radiographic studies were carried out. All identified orthopedic injuries were stabilized by plaster splinting or traction, and 14 climbers were then transferred by helicopter or ground transportation to receiving hospitals where definitive surgical interventions occurred.

Fatalities

Of 220 climbers injured in Yosemite during the study period, 13 died, yielding a case-fatality rate of 6%. In 11 of the 13 fatal cases, death occurred before rescuers arrived. Two fatally injured climbers survived until after arrival at the Yosemite Clinic, one dying of hypothermia and the other of head injuries sustained in a leader fall. Two other climbers died of hypothermia incurred during autumn storms, four others died of head trauma sustained in leader falls, and one died of head injury after rappelling off the end of his rope. Another climber died of abdominal hemorrhage incurred from a rock fall while sleeping, two others fell together 243 m (800 ft) when their belay anchor failed, dying of massive head and internal injuries, and one climber died of head injuries caused by rock fall. The pathologist who did the autopsies on most of the fatalities believes that helmet use

might have prevented some deaths from head trauma (James Wilkerson, MD, oral communication, January 1987).

Discussion

This study has shown that the vast majority of rock-climbing injuries in Yosemite National Park are minor. The large number of self-rescued climbers detected by monitoring the clinic cases in addition to the more severely injured rescued cases contributed dramatically to lowering the median injury severity score for the combined group. This preponderance of low injury severity scores has also been seen among injured climbers in the Grand Tetons.[2]

The pattern of injury among Yosemite climbers is remarkable for frequent injury to the skin or subcutaneous area and to the lower extremities. The high frequency of contusions, lacerations, and abrasions apparently results from the blunt, glancing, or abrasive forces that occur as the climbers fall.

A preponderance of lower extremity injuries has also been documented among injured climbers in the Grand Tetons[2] and in the eastern Sierra Nevada, with trauma in the latter area predominantly to the ankle or distal third of the tibia.[6] Most of the injuries among climbers in the Chamonix-Mont-Blanc region were also to the extremities (56%) and particularly involved ankle fractures.[7] Thus, injured Yosemite climbers tended to have an injury pattern similar to the patterns described from other areas, with the exception of acute mountain sickness, frostbite, and hypothermia, which have occurred with greater frequency in higher, colder climbing regions.

The high frequency of lower extremity injuries among climbers has been attributed to inadequate "isokinetic strength training."[6] We suggest that lower extremity injury is simply a function of a high energy transfer to a small area of the body, regardless of strength, as evidenced by the high incidence of fracture. The high incidence of foot and ankle injuries among injured climbers provides evidence that climbers strike the rock in an upright position as they fall. The rare occurrence of head injury in this study also supports this concept. A similar pattern of injury is also seen in victims of elevator falls and in injured parachutists. Maull and associates described the cases of six victims injured when an elevator malfunctioned and fell three stories to the ground. All six patients sustained fractures below the knee.[12] Ciccone and Richman reviewed 2,709 cases of fractures sustained by parachuting and found 86% of these to be confined to the lower extremities.[13] An urban series of 161 falls from a height also revealed multiple fractures as the most common injury and in the same predictable distribution involving the lower extremities, pelvis, and spine.[14]

Several cases at the shorter fall lengths show why injury severity among injured climbers did not correlate better with length of fall. In one case, a woman fell 30 m (100 ft) while leading a near vertical pitch, and her belayer failed to arrest her fall until the rope jammed in a carabiner. She hit scarcely any rock on the way down, receiving only a small laceration and minimal contusions (ISS 1). When the rope jammed, it decelerated her elastically, imparting no further injury. Modern climbing ropes have an important elastic property: the greater the length of rope between falling climber and belayer, the longer the distance over which the climber is decelerated. In another case, a climber fell only 2 m (6 ft) but smashed into a highly angulated ledge, suffering a compound fracture of the femur and severe abrasions (ISS 13). A third climber fell just 6 m (20 ft) but hit the ground, sustaining a concussion, rib fractures, and a dislocated ankle (ISS 17). In these cases, injury severity may have been determined more by the shape of a rock ledge, the angle of impact, and the body surface area striking rock than by the length of the fall.

The average experience level among injured climbers was high: 60% of injured climbers in Yosemite had more than three years of experience, and 71% of them could lead climbs rated 5.10 or above in difficulty. In contrast, only 21% of those injured climbing in the eastern Sierra Nevada had more than five years of active climbing experience.[6] Similarly, the majority of climbing victims in the Grand Tetons had been climbing less than a year.[2] Only 24% of all injured climbers recorded in American Alpine Club data between 1951 and 1983 had more than three years' experience (H.A.A., unpublished data, compiled May 1986). The high level of experience among injured Yosemite climbers suggests either that relatively few beginners are climbing in Yosemite or that beginning climbers are less often injured than are experienced climbers. Preliminary climber census data support the former explanation (T.K.H., unpublished data, compiled November 1987).

This study documents the lowest case-fatality rate reported to date (6%). This can be contrasted to the case-fatality rate reported among climbers injured on rock in the United States between 1951 and 1960 (41%),[1] in the Grand Tetons (19%),[2] on Mount McKinley (9%),[5] and in the eastern Sierra Nevada (8%).[6] Our results are in accord with another large rock-climbing series in the European literature that found "serious sequelae" in only 4% of 114 rock climbers treated in hospital.[15] In Yosemite, most of the injured climbers found their own way to the clinic. All but one severely injured climber required Park Service rescue. The large discrepancy in ISSs between Park Service-rescued and self-rescued case groups supports the hypothesis that many earlier studies have overrepresented severely injured cases by relying on search and rescue data. Furthermore, some injured climbers undoubtedly left Yosemite unrecorded, to receive medical care at home. Including these "drive-aways" would have lowered our median ISS still further.

The isolated nature of most climbing accidents impairs a rapid and definitive medical intervention. Nonetheless, at the Yosemite Clinic, the outcome among severely injured climbers was probably not adversely affected by the lack of capability for extensive surgical intervention or blood transfusions. All but one person who would have benefited by such interventions died before rescuers could reach them. In the one case of hypothermic fatality transported to the clinic, immediate access to cardiopulmonary bypass rewarming might have been helpful though impractical. If rescue times are lowered, then the time to surgical intervention and intensive care will also have to be lowered to increase survival.

The injury pattern seen among Yosemite climbers suggests certain ameliorative strategies. Among fatally injured climbers, weather and head injuries played predominant causal roles. Head injuries, though rare, were often severe. As noted by the park's pathologist, using a helmet might have prevented some deaths. Nonetheless, international standards only require helmets to withstand impact energies equivalent to that generated by a 5-kg object falling 2 m onto a helmet,[16] similar to a relatively short fall. Also, because head trauma is

a rare event, helmet use would have to become almost universal to significantly reduce mortality.

The frequent occurrence of abrasions or lacerations might be ameliorated by the use of tough, durable clothing. Efforts to reduce lower extremity injury could include devising shoes to absorb and diffuse impact. Unfortunately, climbers complain of overheating and restriction of movement caused by excess clothing, and bulky shoes are considered unacceptable. Careful attention to weather forecasts and preparation with equipment for inclement weather could reduce morbidity and mortality due to hypothermia, even in a rarely snowy environment like Yosemite.

The Injury Severity Score was a useful tool for the study of climbing injuries. All climbing injuries, except hypothermia, could be scored using the Abbreviated Injury Scale, originally designed for motor vehicle and highway-related injuries.[10] The ISS successfully distinguished between the more severely injured climbers requiring rescue and the less severely injured, self-rescued climbers. We would hypothesize that AIS scores—and therefore ISS—could be applied to hypothermic patients also, if fatality rates for values of a suitable diagnostic marker, such as core temperature, could be established for a large sample of cases. The ISS appears useful to compare preventive, rescue, and medical intervention systems of different regions where climbing injuries occur.

Conclusion

This study shows that the typical rock-climbing injury in Yosemite National Park was a nonfatal injury to the lower extremities with associated superficial injuries. Injury typically occurred in a highly experienced, usually male, climber who fell while leading a climb. Injury severity scoring was a useful tool to document the minor severity of most injuries. Most fatalities were due to head trauma or hypothermia. Rescue personnel had to manage airways successfully in head-injured victims, anticipate and treat complications of hypothermia, and stabilize frequent fractures. The receiving medical clinic was required to secure airways and ventilation, establish adequate circulation, identify and stabilize orthopedic and associated injuries, and prepare some patients for transport to definitive facilities. The rural clinic could adequately stabilize nearly all cases of climbing injuries because victims requiring immediate surgical intervention or blood transfusion usually died before rescue could be effected.

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Clinical Medicine

Rates and Causes of End-Stage Renal Disease in Navajo Indians, 1971-1985

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The rates of end-stage renal disease are much increased in American Indians, but no longitudinal study of its rates and causes has been undertaken in any tribe. This 15-year study of rates and causes of treated end-stage renal disease in the Navajo, the largest Indian tribe, supplies an important model on which to base projections and plan interventions. Treated end-stage renal disease in Navajos has increased to an age-adjusted incidence 4 times that in whites in the United States. Diabetic nephropathy accounted for 50% of all new cases in 1985, with an incidence 9.6 times that in US whites, and was due entirely to type II disease. Glomerulonephritis caused end-stage renal disease in Navajos at a rate at least 1.8 times that in US whites and afflicted a much younger population. The predominant form was mesangial proliferative glomerulonephritis associated with an immune complex deposition. Renal disease of unknown etiology, which probably includes much silent glomerulonephritis, accounted for 20% of all new cases. The aggregate Navajo population with end-stage renal disease was 9 years younger than its US counterpart.

These observations reflect the genesis of the epidemic of diabetic nephropathy afflicting many tribes. Urgent measures are needed to contain this. In addition, the etiology and control of mesangiopathic, immune-complex glomerulonephritis of unusual severity, a previously unrecognized problem, need to be addressed.

(Megill DM, Hoy WE, Woodruff SD: Rates and causes of end-stage renal disease in Navajo Indians. West J Med 1988 Aug; 149:178-182)

Renal disease and renal failure among American Indians of the Southwest are causing much morbidity and generating huge costs for the provision of health care. Disease control and planning for future facilities to treat end-stage renal disease depend on an understanding of the patterns of renal disease and failure in these populations. No longitudinal studies of rates or causes of end-stage renal disease in American Indians in general, or in any individual tribe, have been reported, however.

The Navajos are the largest Indian tribe in the United States, with an estimated 1986 population of 181,150—almost a quarter of all reservation Indians in this country.[1] The Navajo share many characteristics with other Indian tribes. These include recent changes in health and life-style associated with their adopting westernized culture and habits, and recently prolonged life spans, which permit greater manifestations of chronic disease processes. The consequences in Navajos mirror to some extent those experienced by other tribes.

Perceptions of one of us (D.M.M.) of changing rates and causes of end-stage renal disease in Navajos, acquired through 12 years of caring for patients with renal disease and renal failure, led to this formal study.

Methods

Data for this report were gathered from three sources. The first was the records of the End Stage Renal Disease Network 6 registry in Albuquerque. The registry maintains identification of patients by race and zip code, but not by tribe. The second source consisted of the records maintained by the Indian Health Service (IHS) in Shiprock, New Mexico, of most Navajo patients beginning dialysis. The third source comprised the clinical records maintained by one of us (D.M.M.) and was the most comprehensive. These records include only patients in whom therapy for end-stage renal disease was initiated and thus underestimate the total disease load. All comparative data are subject to the same qualification. The cross-referenced data sources, the contained nature of the IHS health delivery system, and the limited number of nephrologists who have cared for the Navajo make this one of the most accurate longitudinal surveys of end-stage renal disease in any group in the United States. Navajo population statistics were supplied by the tribal statistician and demographer. They assume populations of 107,000, 130,000, 150,000, and 170,000 in 1970, 1975, 1980, and 1985, respectively, and growth rates of 3.52%, 3.07%, and 2.67% in the intervals of 1971-1975,

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ABBREVIATIONS USED IN TEXT

HCFA = Health Care Financing Administration
IHS = Indian Health Service

1976-1980, and 1981-1985, respectively. These figures apply to Navajo Indians on the main reservation, Ramah, Canoncito, and Alamo satellite reservations, and Navajos who have tribal census numbers and live in the border areas surrounding the reservation. High birth rates in Navajos have resulted in a youthful population; 50% of the Navajos are younger than 18 years, while only 26.4% of the total US population is younger than 18.

Comparative local data are derived from the 1985 report of the End Stage Renal Disease Network 6 Registry.[2] The data for the US population are derived from the End Stage Renal Disease Patient Profiles for 1985, compiled by the Office of Management and Statistics of the Health Care Financing Administration (HCFA).[3] Mean ages of the US population with end-stage renal disease were supplied at our request by the Director of Information Analysis in that organization. The HCFA data include only patients enrolled in the Medicare program and thus underrepresent the population with end-stage renal disease by perhaps 2% to 10%, as informally estimated by HCFA. US census data were obtained from the Data Bank at the University of New Mexico, Albuquerque.

The changes in the age characteristics of the Navajo and the US population, and the discontinuity and changes in the US-wide renal disease data banks over this 15-year period, make longitudinal age-matched comparisons of Navajo and US end-stage renal disease rates inaccurate. Age-adjusted Navajo rates compared with the aggregate and white US populations were calculated for the year 1985, however. Age-adjusted mortality calculations were invalidated by similar considerations and by the small number of Navajos in each disease category who died in any one year.

Except where specified, incidence and prevalence rates are expressed as cases per million. "Prevalence" was calculated from the number of living patients being treated for end-stage renal disease on December 31 each year. This was compared with "point prevalence" in the HCFA US data.

Patient selection criteria for treatment have undoubtedly changed over the period of review, being especially liberalized by the introduction of Medicare coverage for such treatment in July 1973. In the early 1970s there were no dialysis units on the Navajo Reservation and patients were flown to units in Albuquerque, Phoenix, and Denver for treatment. In 1985 there were dialysis facilities in Gallup and Farmington, New Mexico, and Chinle and Tuba City, Arizona—all serving the Navajo population. Transportation problems have thus been reduced, although some Navajos are still flown to and from dialysis. Similar changes in selection criteria and availability of facilities have influenced treatment of the general US end-stage renal disease population over this time.

Most Navajos being treated for end-stage renal disease receive in-center hemodialysis. Continuous ambulatory peritoneal dialysis was introduced in 1982. In 1985 there were 104 patients receiving hemodialysis and 15 patients receiving continuous ambulatory peritoneal dialysis.

The diagnoses of the causes of end-stage renal disease were based on the usual criteria. Diabetic renal disease was diagnosed when high levels of proteinuria and renal insufficiency developed in the presence of diabetic retinopathy and a long history of diabetes mellitus, and there were no indications of another disease process. These patients rarely had a biopsy, so that other renal diseases could be obscured in this group. Diabetes mellitus causing nephropathy was uniformly of the type II variety in the Navajo series. Glomerulonephritis was diagnosed on the basis of a compatible clinical picture, with hematuria, proteinuria, and sometimes hypertension, and was confirmed by renal biopsy in 34 of the 75 cases. This category included glomerulonephritis due to systemic lupus erythematosus and to Henoch-Schönlein purpura. "Other" renal disease included chronic infectious pyelonephritis, tuberculous pyelonephritis, urinary tract obstruction, familial renal tubular acidosis (three cases), hypertensive renal disease (two cases), and various other conditions. Persons with "unknown" renal disease usually presented with severe renal insufficiency, with few prior symptoms and no features of specific disease processes. They usually had small kidneys and for this reason or other relative contraindications did not undergo renal biopsy. This category probably includes many cases of glomerulonephritis. Biopsy philosophies may have resulted in some segregation of older people into this group.

Approval of the Navajo Area Indian Health Service Research and Publications Committee was obtained for this study, with the provision that no patient be identified by name in the reporting.

Results

Table 1 shows the incidence and prevalence of end-stage renal disease in Navajos for each year of the period under review. Both have risen dramatically. The absolute incidence and prevalence for 1985 were 2.1 and 3 times those of US whites. (As discussed later, the age-adjusted rates were even higher.) The Navajo rates similarly exceeded those of whites and Hispanics in Network 6.

The trends in end-stage renal disease in Navajos are shown in Table 2, in which average annual rates for each five-year period are compared. The increases in incidence and prevalence between each interval are statistically significant.

TABLE 1.—*Rates of End-Stage Renal Disease in Navajos, 1971-1985*

	Year														
Cases and Rates	*1971*	*1972*	*1973*	*1974*	*1975*	*1976*	*1977*	*1978*	*1979*	*1980*	*1981*	*1982*	*1983*	*1984*	*1985*
New cases, No.	2	7	2	3	10	12	18	19	19	21	27	19	41	29	30
Incidence, per million	18	60	16	24	77	82	130	134	130	139	175	120	253	174	176
Patients receiving treatment, No.	3	6	6	9	18	27	39	38	46	51	66	69	96	109	119
Prevalence, per million	27	52	51	73	139	202	283	266	314	340	429	436	591	654	700

The average incidences for the four major disease categories in each five-year period are shown in Table 3. Although only the increase in diabetic nephropathy between 1976-1980 and 1981-1985 is statistically significant, an increasing trend in the unknown etiology category is also evident.

Table 4 shows the proportion of the end-stage renal disease burden due to each of these four major categories in 1985. The major contributions of diabetic renal disease, disease of unknown origin, and glomerulonephritis are evident.

Table 5 compares the 1985 Navajo incidence of end-stage renal disease with those of the aggregate US population and the US white population, using age-adjusted rates. The Navajo incidence of diabetic nephropathy was 7.4 and 9.6 times the incidences in these respective populations, the incidence of glomerulonephritis-associated end-stage renal disease was 1.6 and 1.8 times their respective rates, and the overall incidence of end-stage renal disease was 3.1 and 4 times their rates. There is no category in the US data comparable to the "unknown etiology" used for the Navajos, but the 1985 incidence of end-stage renal disease of undesignated cause in the US aggregate population was only seven cases per million. The paucity of hypertensive renal disease in Navajos is in dramatic contrast to the situation in the aggregate US population, where hypertensive renal disease constitutes 25% of the incident cases of end-stage renal disease. No case of renal failure due to polycystic kidney disease had been diagnosed in Navajos up to the end of 1985.

Of 75 subjects with glomerulonephritis-associated end-stage renal disease, clinical diagnoses included poststreptococcal glomerulonephritis in 2, systemic lupus erythematosus in 5, Henoch-Schönlein purpura in 6, and Goodpasture's disease in 1. Of 27 renal biopsies available for us to reevaluate, 17 (63%) showed mesangial proliferative, immune complex-associated glomerulonephritis, 3 in a setting compatible with Henoch-Schönlein purpura; 5 (19%) were compatible with lupus glomerulonephritis, as suggested by their history and clinical findings; and 5 (19%) showed other pathologic processes.

Table 6 shows the disease-specific mean ages of Navajo patients at the start of treatment. Those with diabetes mellitus were significantly older than patients in all other categories. The wide ranges of ages in the "unknown" and "other" categories of disease are consistent with multiple causes in both groups.

Table 7 compares the age of the entire Navajo patient population at the start of treatment with the age of the 1985 US incident population. The average age of Navajo patients with end-stage renal disease was nine years less than that of the US patients. There was a striking difference in the ages of Navajo and US patients with end-stage renal disease due to glomerulonephritis. The fact that all nephropathy in Navajos with diabetes is due to type II disease is reflected in the

TABLE 2.—*Average Annual Rates of End-Stage Renal Disease in Navajos, Cases per Million*

5-Year Period	Incidence, Mean ± SD		Prevalence, Mean ± SD	
1971-1975	39.0 ± 27.7	$P<.005$	68.4 ± 42.5	$P<.005$
1976-1980	122.8 ± 23.1	$P<.01$	280.8 ± 52.5	$P<.005$
1981-1985	179.4 ± 47.3		562.0 ± 124.5	

SD=standard deviation

TABLE 3.—*Disease-Specific Changes in the Incidence of End-Stage Renal Disease (ESRD) in 1971-1985, Average Annual Incidence per Million**

	Cause of ESRD			
5-Year Period	Diabetes	Glomerulonephritis	Diagnosis Unknown	Other
1971-1975	3.2 ± 4.4	14.4 ± 21.4	10.0 ± 16.2	1.5
1976-1980	49.0 ± 13.5	37.4 ± 26.2	31.0 ± 22.3	9.6 ± 10.5
1981-1985	80.0 ± 28.6†	35.6 ± 12.9	50.5 ± 19.2	10.3 ± 8.7

*Mean ± standard deviation.
†$P<.05$ compared with 1976-1980.

TABLE 4.—*Disease-Specific Contributions to Rates of Treated End-Stage Renal Disease (ESRD) in Navajos in 1985*

Cause of ESRD	Proportion of Incidence, %	Proportion of Prevalence, %
Diabetes mellitus	50.0	39.5
Unknown	20.0	25.2
Glomerulonephritis	16.7	32.8
"Other" causes	13.3	5.0

TABLE 5.—*Comparison of Navajo End-Stage Renal Disease (ESRD) Incidence With the Aggregate US and US White Population Incidences, Age-Adjusted Rates: Cases per Million, 1985*

	Population Incidence	
Cause of ESRD	Aggregate US	Navajo
Diabetes mellitus	28	210
Glomerulonephritis	22	34
All causes	103	317
	US White	Navajo
Diabetes mellitus	23	220
Glomerulonephritis	19	34
All causes	83	331

TABLE 6.—*Age at Start of Treatment for End-Stage Renal Disease (ESRD) in Navajos, by Disease Category**

	Navajo Patients	
Cause of ESRD	No.	Mean Age ± SD, yr
Diabetes mellitus	102	58.4 ± 10.3
Unknown etiology	65	49.4 ± 18.4
Other causes	16	47.7 ± 20.5
Glomerulonephritis	75	37.1 ± 17.0

SD=standard deviation

*Diabetes *v* all other categories: $P<.005$.

TABLE 7.—*Ages of Navajo and US Incident Patients With End-Stage Renal Disease (ESRD) at Start of Treatment*

	Navajo		US Aggregate, 1985	
Cause of ESRD	No.	Mean Age ± SD, yr	No.	Mean Age ± SD, yr
All	259	47.4 ± 19.0	24,624	56.3 ± 17.5*
Glomerulonephritis	75	37.1 ± 17.0	5,216	53.4 ± 19.0*
Diabetes mellitus	102	58.4 ± 10.3	6,785	54.9 ± 14.7*

SD=standard deviation

*Navajo *v* US aggregate: $P<.001$.

TABLE 8.—*Average Annual Mortality of Navajo Patients With End-Stage Renal Disease (ESRD) by Disease Category*

Cause of ESRD	5-Year Period 1976-1980, %	1981-1985, %	P Value
Diabetes mellitus	31.4	21.9	NS
Unknown	23.3	15.4	NS
Other	17.6	14.3	NS
Glomerulonephritis	14.7	6.9	NS
All subjects	22.4	15.7	<.05

NS=not significant

greater mean and narrower range of ages in this group than in the US diabetic population with end-stage renal disease.

Disease-specific actuarial survivals of Navajo patients after the start of treatment were calculated by cohort. Mean survivals were 24 months for patients with diabetes, 39 months for patients with renal disease of unknown etiology, 39 months for those in the "other" category, and 103 months for those with glomerulonephritis. The much longer survival of patients with glomerulonephritis explains the greater contribution of this group to the prevalence of end-stage renal disease than to its incidence.

The average annual mortality rates for each disease category and for the entire Navajo renal disease population for the last two 5-year periods are shown in Table 8. These confirm the different mortality rates among the disease categories from the actuarial survival calculations. Survival has improved in each disease category, although the difference was significant only for the population as a whole. These mortality rates compare favorably with those of the 1985 US population with end-stage renal disease, of 16.7% for the aggregate population, and 11.5% and 21.9%, respectively, for those with glomerulonephritis and diabetes.[3]

A total of 37 renal transplants were carried out on 35 Navajo recipients: 17 of the recipients had glomerulonephritis, 11 had end-stage renal disease of unknown etiology, and 7 had it of other causes. In all, 15 transplants were from cadaveric donors and 22 were from living related donors. Most transplants were done before the cyclosporine era. Actuarial two-year graft survivals after transplant, calculated by cohort, were 40% and 86% for recipients of cadaveric kidneys and living related kidneys, respectively, and two-year patient survivals were 58% and 90%, respectively. These are probably comparable to national data spanning 15 years of transplantation in the precyclosporine era.

Discussion

The rates of treated end-stage renal disease in Navajos have increased progressively over the past 15 years. The changes over the first few years may partly reflect increased identification of cases as access to treatment improved. It also appears, however, that a real increase in the rates of end-stage renal disease has occurred, at least in the past ten years, when access to treatment has not been a limiting factor.

The current case load is largely due to diabetic nephropathy, renal disease of unknown etiology, and glomerulonephritis—all of formidable proportions. Despite the preponderance of patients with type II diabetes, Navajo patients are younger than the aggregate US population with end-stage renal disease.

Although Navajos do not have the highest population-adjusted rates of end-stage renal disease among Indians, they have the largest number of persons on dialysis by virtue of the size of the tribe, and these rates appear to still be rising.

The increase and current preponderance of diabetic renal disease in Navajos, all due to type II diabetes, is striking. Type II diabetes mellitus and pathologic obesity were almost nonexistent in Navajos several decades ago, and in the 1930s only five persons with diabetes were recognized among 25,000 hospital admissions to Sage Memorial Hospital serving Navajos in Ganado, Arizona.[4] This is in stark contrast to the situation today. The Navajo and most other Indian tribes are now experiencing a pandemic of type II diabetes, related to diet and life-style changes, probably in the setting of a genetic predisposition.[5] Many Navajos are obese, and type II diabetes and diabetic nephropathy are being diagnosed with increasing frequency. Diabetic renal disease is responsible for 39.4% of Navajo cases of end-stage disease since 1971, 44.5% of all patients whose treatment started in the past five years, and 50% of all patients whose treatment started in 1985. New cases are arising at an age-adjusted rate 9.6 times that in US whites, and rates appear to be still rising.

The prevalence and complications of diabetes in Navajos have not yet reached the proportions seen in Pima, Papago, and Zuni Indians.[6,7] In the early 1980s, the prevalence of end-stage renal disease in Pimas and Papagos was eight times the aggregate for Network 6, and 90% of Pima and 72% of Papago cases were attributed to diabetes.[6] In 1985 the prevalence of end-stage renal disease in the Zunis was 17 times that in US whites, 38.5% attributed to diabetes.[7] These tribes, however, are much smaller than the Navajo, whose large population generates, even at the current rate of diabetes, by far the greatest load of diabetic nephropathy of any tribe. If Navajo diabetes rates are merely trailing rates of these other tribes by a few years, the potential load of diabetic renal disease in the future could be formidable.

Only a swiftly implemented and effective program of exercise, diet, and life-style changes will alter this epidemic of type II diabetes. A model program in Zuni Indians has produced dramatic short-term results,[8] but the effects on long-term diabetic complications and end-stage renal disease rates remain to be determined. Modifying the progression of renal insufficiency in patients with established diabetic nephropathy is an imperative short-term goal, therefore.

Glomerulonephritis produces renal failure at greater rates in the Navajo than in the aggregate US and the US white populations, at a much younger age, and with a preponderance of idiopathic mesangial immune-complex disease. This is consistent with findings in a separate study of the same process in 71% of all renal biopsy specimens from American Indians from New Mexico and northeastern Arizona, compared with only 23.6% of biopsies in non-Indians.[9,10] The mean age of afflicted Indian patients at biopsy was 32 years, and the disease was unusually aggressive. Pronounced familial clustering of this disease was noted in the Zunis, and familial patterns were suggested in the Navajo and other Indian groups.[7,10] The dominance of this very aggressive disease accounts for the striking disparity in ages between the Navajo and US populations with glomerulonephritis-associated end-stage renal disease. This same disease is probably the major cause of the "unknown etiology" category as well, because idiopathic glomerulonephritis is the most common renal disease that can lack specific clinical signs and remains asymptomatic until the preterminal phase.

As a result, the rates of glomerulonephritis-associated end-stage renal disease in the Navajo are probably much higher than calculated here and could still be rising.

The scarcity of cases of polycystic disease in Navajos is undoubtedly due to their genetic makeup. Likewise, no cases of polycystic disease have been seen in Zunis.[7,11] The low prevalence of primary hypertensive renal failure in Navajos may change as the prevalence of hypertension, one of the results of acculturation, increases.

The different survival rates among the various disease categories in Navajos with end-stage renal disease deserve comment. The high mortality rate in patients with diabetes is probably a function of their greater age and multisystem disease, while the excellent survival rates of those with glomerulonephritis reflect their younger ages and general good health, except for renal disease. The intermediate survivals of patients in the unknown and "other" categories probably reflect their mix of disease processes and patients' ages.

The survival rates of the Navajos with treated end-stage nephropathy from 1981 to 1985 are excellent, considering the wide geographic dispersion of the Navajo tribe, harsh physical and climatic conditions, poverty, problems with transportation, and the high proportion of persons with diabetes in the renal disease population. Improved mortality rates, however, increase the total end-stage renal disease load and thus the costs of treatment.

Projections of the future burden of end-stage renal disease in Navajos depend on the age structure of the Navajo population, the evolution of the epidemic of type II diabetes, survival rates with treatment of end-stage disease, rates of successful transplantation, and the development of strategies to retard the progression to renal failure in patients with renal disease of any cause. The burden seems likely to increase over the next decade, however, as the large cohort of youthful Navajos ages, diabetes mellitus and its complications develop, and more Navajos become susceptible to the renal diseases associated with aging, such as occur in the composite US population.

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Ear Examination

I DO MY EAR EXAMINATION with the child sitting up on the mother's knee. I think most doctors probably do it with the child lying down. Nine times out of ten, when the child, even a little baby, is sitting on the mother's knee, I can get a nice look at the ear without upsetting the child. When the mother asks "Why didn't he cry?" I tell her that at the pediatrician's office when children lie down on that table, they are used to getting jabbed. They're already programmed. So as soon as they lie down, they start crying.

—ROBIN T. COTTON, MD

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Screening for Hepatocellular Carcinoma
Review and Perspective

JONATHAN C. ELLIS, MD, *Los Angeles*

In patients with hepatocellular carcinoma, early diagnosis offers the only hope for resection and cure. Data from Asia, where it is closely associated with viral hepatitis, indicate that serum α-fetoprotein assay and abdominal ultrasonography are the most effective and feasible screening tests. These data may not be applicable in America, where most patients at risk for hepatocellular carcinoma have underlying alcoholic cirrhosis. Also, it is unclear whether resecting "curable" lesions prolongs survival, particularly in patients with cirrhosis. Screening trials are indicated to answer these questions. Preventing risk factors, however, especially hepatitis B viral disease, is of paramount importance throughout the world.

(Ellis JC: Screening for hepatocellular carcinoma—Review and perspective. West J Med 1988 Aug; 149:183-187)

Hepatocellular carcinoma (hepatoma) accounts for 90% of all primary liver carcinomas.[1] It is one of the most common malignant disorders in Japan,[2,3] Taiwan,[4] and other areas of Asia and Africa.[5-8] Hepatocellular carcinoma is heterogeneous in its pathogenesis, clinical presentation, virulence, and prognosis. In the United States and Western Europe, greater than 90% of hepatomas arise in the presence of alcoholic cirrhosis.[2,4,9-11] In the "hepatic-cancer belt" of Asia and Africa and in the Pacific Islands, as many as 80% of patients with this malignant disorder are positive for the hepatitis B surface antigen (HBsAg) and as many as 40% do not have cirrhosis.[9] In areas endemic for hepatitis B, such as Taiwan, where the HBsAg carrier rate is as high as 15% to 20%, there is overwhelming evidence tying chronic carriage of HBsAg to hepatocellular carcinoma.[12-14] Perinatal transmission is responsible for as many as 40% of carriers. Moreover, up to 90% of infants born to mothers positive for the hepatitis B e antigen become carriers.[15] These patients have a greater than 200-fold risk of hepatoma developing in early adulthood and middle age.[16] With the recent influx of nearly 1 million Southeast Asian refugees, there will be a substantial increase in this country of those at risk for hepatocellular carcinoma.[17] This will add a new dimension to the pressing need for an organized approach to preventing and treating the disorder.

Resection offers the only hope for cure. Resectability is determined by the location and size of the tumor, symptoms, extent of local spread, and severity of underlying liver disease.[11] Screening programs predicated on the assumption that it is essential to find the tumor as early as possible have produced disparate results.[2,8,18-20] This may be due to the diverse nature of the carcinoma, the varying availability of medical care, the use of different screening regimens, and problems with patient compliance.

A full understanding of available screening modalities may guide decisions regarding their use in patients at risk for hepatocellular carcinoma.

Available Screening Tests

α-Fetoprotein Level

α-Fetoprotein is a serum protein found in high concentrations in fetal and maternal blood. Normal levels range from 0 to 5 ng per ml. Levels of 15 to 25 ng per ml and above are considered significantly elevated. Levels as high as, but rarely exceeding, 200 ng per ml may occur with chronic liver disease, hepatic regeneration, and tumors other than hepatocellular carcinoma. Concentrations of greater than 200 ng per ml increasingly suggest hepatoma. Specificity for the disorder is high at levels above 400 ng per ml.[21] The serum α-fetoprotein value is normal in 40% to 60% of patients with hepatocellular carcinoma in the US and Europe.[21,22] The correlation between the disorder and elevated α-fetoprotein levels is stronger in young male patients and in those with underlying hepatitis B viral disease. Serum concentrations generally parallel the size of the tumor and are often normal in "early" or "minute" (2 to 4 cm) hepatoma.[2]

Measurement of serum α-fetoprotein levels has been used for mass screening for hepatocellular carcinoma in Africa, Japan, and China. Okuda notes that screening programs in Africa failed to identify asymptomatic patients despite the strong association between hepatitis B-related hepatoma and α-fetoprotein levels.[8] This may be due to the undifferentiated, virulent nature of the disorder in this area. In China, where hepatocellular carcinoma tends to grow more slowly, Beasley and co-workers have documented the epidemiologic association between the hepatitis B virus and hepatoma.[16,23] Mass screening of 1.9 million people in Shanghai during 1971 to 1976 resulted in the identification of 300 patients with hepatocellular carcinoma, 134 of whom were asymptomatic.[24] Diagnosis resulted from a "positive" α-fetoprotein level—greater than 500 ng per ml in this study. Of these, 31 had resectable tumor, with a 57% three-year survival. Using α-fetoprotein assay in another mass screening of 1.2 million people in Qidong, Zhu identified

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
HBsAg = hepatitis B surface antigen

475 patients with hepatocellular carcinoma, 35% of whom were asymptomatic.[25]

Table 1 summarizes data from prospective studies. Heyward and colleagues screened 1,394 HBsAg-positive Alaskan Natives using serial α-fetoprotein assays.[18] Levels were greater than 25 ng per ml in 126. Nine had proven hepatocellular cancer. In all of these patients, α-fetoprotein levels were greater than 350 ng per ml. Six were asymptomatic and four had resectable tumor with curative intent. Liaw and associates screened 432 HBsAg-positive patients with α-fetoprotein assay and ultrasonography every three to six months, finding eight patients with asymptomatic hepatoma over a follow-up period of 6 to 85 months. Three cases were diagnosed by α-fetoprotein levels of greater than 400 ng per ml, while three were "suggested" by levels of 100 to 300 ng per ml. Two patients had "negative" levels—less than 20 ng per ml—and hepatoma was diagnosed by ultrasonogram.

Kobayashi and associates prospectively screened 95 persons with cirrhosis of mixed cause, doing α-fetoprotein assays every two months, an abdominal ultrasonogram every three months, and computed tomographic (CT) scan with angiography yearly.[2] Over a mean period of 4.2 years, eight cases of hepatocellular carcinoma were detected. Three patients had normal (less than 25 ng per ml) α-fetoprotein levels, two had "nondiagnostic" levels (less than 200 ng per ml), and only three had levels greater than 400 ng per ml. None of the tumors were resectable.

Obata and co-workers observed 115 patients with cirrhosis for as long as four years with serial α-fetoprotein assays every two months.[26] Ultrasonography, scintigraphy, and angiography were used as confirmatory tests when an α-fetoprotein level was elevated. Hepatocellular carcinoma developed in 27% of HBsAg-positive cirrhotic patients and in only 6% of seronegative patients with cirrhosis, underscoring the link between hepatitis B and hepatocellular carcinoma. The number of asymptomatic and resectable cases is not reported. Kubo and associates reported 31 cases of the disorder detected over a 1- to 14-year follow-up of at least 400 patients with chronic liver disease.[27] The α-fetoprotein level was a sensitive and specific marker, being greater than 400 ng per ml in 19 patients, more than 1,000 ng per ml in 16, and less than 400 ng per ml in only 6. But the majority were symptomatic at the time of diagnosis, and the smallest tumor detected by α-fetoprotein assay was 4 to 5 cm in diameter. The authors note that most patients were followed up sporadically, making any conclusion regarding the sensitivity of α-fetoprotein assay for detecting asymptomatic or treatable disease in these patients problematic.

The failure of α-fetoprotein assay to detect treatable disease in Japanese trials, along with other studies finding a poor correlation between α-fetoprotein levels and resectable hepatoma,[27-30] has led Japanese investigators to conclude that while α-fetoprotein levels may disclose asymptomatic hepatocellular carcinoma, the assay rarely detects treatable disease.[2,8,31,32] Larger prospective trials are warranted, however, especially in populations with a higher prevalence of alcoholic cirrhosis and chronic liver disease unrelated to hepatitis B. Mass screening in China and the work of Liaw and Heyward suggest that serial α-fetoprotein assays may detect asymptomatic and treatable disease in populations with a high incidence of underlying hepatitis B viral disease.

Ultrasonography

Several prospective studies from China and Japan indicate that ultrasonography may be more sensitive than α-fetoprotein assays for detecting resectable hepatocellular carcinoma, though the number of patients in these studies is small.[2,20] In a nonprospective evaluation of 230 asymptomatic patients with chronic liver disease, Okasaki and colleagues found 14 with hepatocellular carcinoma.[19] Seven of the tumors were smaller than 5 cm in diameter. Ultrasonography identified six of these, with a sensitivity and specificity of 86% and 99%, respectively. α-Fetoprotein values were greater than 400 ng per ml in only two of the patients with a lesion smaller than 5 cm. Maringhini and co-workers recently reported their study of 363 patients with cirrhosis and clinically suggestive hepatocellular carcinoma[33]; 146 proved to have the disorder. Ultrasonography showed a sensitivity and specificity of 90% and 93%, respectively. The sensitivity and specificity of an α-fetoprotein level of greater than 500 ng per ml were 49% and 100%, respectively. Of the 56 patients with carcinomatous lesions smaller than 5 cm, 91% were detected by ultrasonography and only 46% by α-fetoprotein assay, though resectability is not reported. Table 2 summarizes the above data.

Kobayashi and associates note that ultrasonographic accuracy is poor immediately below the diaphragm, especially in the superolateral aspect of the right hepatic lobe.[2] When a lesion is less than 2 cm and nonencapsulated, differentiating from hemangiomas, solitary regenerative nodules, or adenomas becomes problematic. In Japan, however, small carcinomas are frequently encapsulated and hypoechoic, making them more easily identifiable.[8,19] The Japanese have reported

TABLE 1.—*Screening for Hepatocellular Carcinoma (HCC)—Prospective Studies*

Source	Persons Screened, No.	Mean Screening Period, mo	HBsAg-Positive, %	Has Cirrhosis, %	HCC Identified, No.
Liaw et al, 1986[20]	432	27	100	<50	8
Heyward et al, 1985[18]	1,394	26	69	Unknown	9
Kobayashi et al, 1985[2]	95	50	35	100	8
Obata et al, 1980[26]	115	35	26	100	12

HBsAg=hepatitis B surface antigen

TABLE 2.—*α-Fetoprotein (AFP) Assay and Ultrasonography in the Diagnosis of 'Small'* or Resectable Hepatocellular Carcinoma (HCC)*

Source	HCC Identified, No.	'Small' HCC, No.	'Small' HCC Diagnosed by AFP Higher Than 400 ng/ml, No.	'Small' HCC Diagnosed by Ultrasound, No.
Liaw et al, 1986[20]	8	7	2	7
Kobayashi et al, 1985[2]	8	2	1	2
Heyward et al, 1985[18]	9	4	4	Not reported
Okasaki et al, 1984[19]—nonprospective	14	7	2	6
Maringhini et al, 1984[22]—nonprospective	146	56	26	51

*Less than 5 cm in diameter.

success in screening large numbers of middle-aged patients with chronic liver disease by using the "human dock" and employing the ultrasonograph as "one of the physical examinations like a stethoscope."[19]

Other Screening Modalities

Before the development of real-time ultrasonography, the only alternative to angiography was radiocolloid scintigraphy, which is relatively insensitive for hepatoma smaller than 3 cm.[8]

Sensitivity and specificity of CT scanning approximate that of ultrasonography because of the occasional presence of isodense tumors.[2,31] Angiocomputed tomography and infusion hepatic angiography provide more sensitivity, but invasiveness, expense, and radiation exposure limit their use to confirming possible neoplasms.[2]

Magnetic resonance imaging is useful in distinguishing hepatocellular carcinoma from small hemangiomas,[8,32] though its sensitivity in diagnosing the disorder is unknown and its expense considerable.

Laparoscopic sonography and biopsy have been used to diagnose hepatocellular carcinoma, though invasiveness prohibits their use as screening tests.

Des-γ-carboxy prothrombin accumulates in the absence of vitamin K or when vitamin K-dependent carboxylase activity is antagonized by the use of warfarin. Liebman and colleagues[34] and Soulier and co-workers[35] found significantly elevated des-γ-carboxy-prothrombin levels in 90% and 74%, respectively, of patients with known hepatocellular carcinoma. Des-γ-carboxy-prothrombin levels were most often normal or insignificantly elevated in cases of cirrhosis, chronic active hepatitis, and metastatic disease, suggesting a possible specificity for hepatocellular carcinoma. Still, it is unclear whether abnormal prothrombin is released because of derangements within the tumor or because of acquired carboxylase deficiency associated with severely impaired hepatic function.[36] As of yet, conclusions cannot be drawn regarding the sensitivity or specificity of des-γ-carboxy prothrombin in detecting treatable hepatocellular carcinoma.

Perspective—Will Early Identification Make a Difference?

The question of the resectability of hepatocellular carcinomas has been addressed by Ronald Malt:

> Since most hepatic-cell carcinomas in the Western Hemisphere arise as multicentric neoplasms in persons with alcoholic cirrhosis, no operation to remove them is reasonable, because of the extent of disease, the poor hepatic reserve, and the presence of portal hypertension.[11]

He adds, however,

> three categories of carcinoma must be considered for aggressive resection: carcinomas [resulting] from sex-hormone therapy . . .; localized carcinomas in patients with good hepatic function, especially those living in the "hepatic-cancer belt" of Africa and Asia; and some "minimal" hepatic carcinomas, even those in cirrhotic patients.

Lin and associates report that of 33 patients with cirrhosis who underwent resection of hepatocellular carcinoma, postoperative hepatic failure developed in 40% (13), and two thirds of those who underwent right lobectomy died of hepatic failure.[37] They attribute these results to poor hepatic reserve and the inability of the cirrhotic liver to undergo compensatory hypertrophy.

Nagasue and co-workers resected hepatomas in 118 patients, 101 of whom had cirrhosis[10]; 70% were Childs's class A. Most tumors were "minimal"—less than 3 cm in diameter—possibly showing the efficacy of Japan's screening programs. The two- and four-year survival rates of nearly 80% in patients without cirrhosis approximated the 88% three-year survival rate in the US series of Fortner and colleagues of 13 noncirrhotic patients who underwent curative resection for hepatocellular carcinoma.[38] Nagasue reported two- and four-year survival rates of 55% and 34%, respectively, in patients with cirrhosis.[10] The series of 109 patients of Lee and associates was divided into 47 symptomatic and 62 asymptomatic patients.[39] The latter group included 89% with cirrhosis and had a four-year survival of 44%. Only 8% of the symptomatic patients survived four years.[39] In Wu and co-workers' series of 180 patients, three- and five-year survival rates were 37% and 16%, respectively.[40]

TABLE 3.—*Operative Mortality and Long-term Survival in Selected Series of Resections of Primary Liver Cancer*

Source	Cases, No.	Cirrhosis Present, %	Survival at 2 Years, %	Survival at 4-5 Years, % (yr)	Operative Mortality, %
Lee et al, 1986[39]					
Symptomatic patients	47	32	52	8 (4)	0
Asymptomatic patients	62	89	80	44 (4)	3
Nagasue et al, 1986[10]	94	86	56	35 (4)	14
Wu et al, 1980[40]	181	70	37	16 (5)	9

Can these data be extrapolated to North American patients with hepatocellular carcinoma, most of whom have underlying alcoholic cirrhosis? Though alcoholic liver disease is still not the major cause of cirrhosis in Japan, it has been increasing dramatically; in one study, 52% of Japanese patients with hepatoma were heavy drinkers.[41,42] While cirrhosis was present in greater than 80% of both Lee's and Nagasue's groups, however, the overwhelming incidence of hepatitis B viral disease in the former and the predominant incidence of chronic viral hepatitis in the latter's population make extrapolating to North American patients problematic. Table 3 summarizes the operative mortality and long-term survival in selected series of patients undergoing resection for hepatocellular carcinoma.

An important concept addressed by Okuda is that a "small" hepatoma is not necessarily an "early" one.[8] Growth rates vary enormously, as described by Sheu and associates, who observed that a 1-cm lesion may take 9.8 months to 10.7 years to reach 10 cm in size.[43] Some hepatocellular carcinomas remain unchanged for many years, and survival for years without treatment is reported.[8]

Ebara and colleagues studied the natural history of minute hepatomas—less than 3 cm in diameter—finding occasional slow growth and a 90% one-year survival, 55% two-year survival, and 13% three-year survival.[44] Their 22 patients were felt to have underlying severe disease (most often cirrhosis) that precluded resection. It is interesting that Nagasue and co-workers also found a 55% two-year survival rate in their patients—most of whom were of a higher Childs's class—who underwent resection for cure.[10] While the latter's three- and four-year survival rates were superior and this comparison does not approximate a randomized, controlled trial, the survival data in patients with resected "minute" hepatomas, particularly in those with cirrhosis, should be interpreted cautiously.

Conclusion

Hepatocellular carcinoma is a diverse disease for which the only cure is resection. The presence of symptoms or a tumor size larger than 6 cm most often indicates unresectability. Serum α-fetoprotein assays and hepatic ultrasonography are effective in identifying asymptomatic, resectable neoplasms in certain populations predisposed to hepatic carcinoma by hepatitis B viral disease.[2,18,20,24,31] Recommended regimens are not well defined, though Kobayashi and associates recommend measuring serum α-fetoprotein levels every two months and doing an ultrasound examination every three months in high-risk Japanese patients.[2] Due, however, to the varying association between serum α-fetoprotein levels and liver disease of different causes and the heterogeneity of hepatomas, these data are not clearly applicable to the majority of American patients at risk for the disorder.

In a recent National Institutes of Health conference, Di Bisceglie and colleagues tentatively proposed measuring α-fetoproteins every three to four months and doing hepatic ultrasonography every four to six months in high-risk patients—including those with replicative hepatitis B infection, cirrhosis, or childhood hepatitis B infection—and doing ultrasonography annually in some lower risk patients.[45] As they noted, these guidelines are not proven but may be justifiable in patients with chronic hepatitis B viral disease. Most Americans at risk for hepatocellular carcinoma, however, have alcoholic cirrhosis. Their inclusion in such a program would incur enormous expense and is not justified, as it is unknown whether such screening will influence therapy or survival.

When small lesions of a suggestive but questionable nature are identified by any means, more frequent serial α-fetoprotein measurements and higher-resolution studies such as CT scanning may be used. Laparoscopic biopsy is indicated in selected cases. A serum des-γ-carboxy-prothrombin level may be a sensitive screening test for hepatocellular carcinoma. Its specificity and sensitivity in identifying asymptomatic, resectable disease are unknown. Four-year survival of greater than 80% has been documented in selected noncirrhotic patients undergoing resection for hepatoma. It is possible to resect hepatocellular carcinoma in patients with cirrhosis, though perioperative and postoperative mortality rates are much higher. Whether resection prolongs survival in patients with cirrhosis is unknown.

Preventing a predisposing factor has become feasible, however. We will see more patients from areas with a high prevalence of chronic hepatitis B viral disease. Physicians should be aware of guidelines regarding screening of patients for hepatitis B surface antigen,[46] especially pregnant women from areas endemic for hepatitis B,[47,48] and recommendations regarding vaccinating persons at risk for chronic infection, especially neonates with HBsAg-positive mothers.[49-52]

Ongoing and future trials may elucidate the role of screening for hepatocellular carcinoma in this country. Only awareness of the pathogenesis and risk factors, however, along with diligence in implementing preventive measures, will reduce the mortality from this disease.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Dubois' Lupus Erythematosus

Edited by Daniel J. Wallace, MD, Assistant Clinical Professor of Medicine, University of California, Los Angeles; Attending Physician, Cedars-Sinai Medical Center, Los Angeles; and Chief Rheumatology Consultant, City of Hope, Duarte, California, and Edmund L. Dubois, MD (Deceased), Clinical Professor of Medicine, University of Southern California School of Medicine, and Director, Collagen Disease Clinic, Los Angeles County-USC Medical Center, Los Angeles. Lea & Febiger, 600 Washington Square, Philadelphia, PA 19106-4198, 1987. 749 pages, $98.50.

This third edition of Dubois' textbook stands as a tribute to the man who fathered this monumental undertaking and who was working on the third edition at the time of his death. Edmund Dubois devoted his professional career to the care of persons with lupus erythematosus in its many varieties and left a heritage of careful clinical observations to guide physicians at all levels of familiarity with this challenging group of illnesses.

Daniel J. Wallace, co-author of this third edition, and Francisco P. Quismorio, Jr, and James R. Klinenberg, Associate Editors, have, with Dr Dubois, produced a volume vastly improved over the revised second edition of 1976. With relatively few other experts, they have provided a thorough review of the historical, epidemiologic, and classification milestones that brought us to our present less than satisfactory overview of this complex family of illnesses. The current concept of an immunologic basis for lupus in humans and in mice is woven through the chapters on "Autoimmunity" and "Animal Models of Systemic Lupus Erythematosus." Although there is still a chapter on the lupus erythematosus cell test, a procedure widely unavailable in part because of its uneconomical resistance to automation, the more widely available serologic tests that frequently aid in diagnosis and management are thoroughly presented. The chapter on "Lupus Anticoagulant and Other Hemostatic Problems" by Rapaport and Feinstein elucidates an area of possible autoimmunity clearly not limited to systemic lupus erythematosus, but one that casts new light on old clinical observations.

Chapters five and seven in particular will be of interest to the widely varied audience of physicians who treat these patients. Sections provide the physician with material for the patient and directed to the problems of coping with a potentially fatal, chronic illness. The chapter on drug management, as well as the discussion of the use of renal biopsy, provide a comprehensive review but leave the readers, appropriately, to make up their own minds in a particular situation.

This third edition strikes this reviewer as a fitting tribute to the life's work of Edmund Dubois and will serve the clinician and clinical investigator with a plethora of suggestions for management and for future clinical investigations, which I am sure would have pleased the senior author.

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Medical Progress

How Physicians Can Help Their Patients Quit Smoking
A Practical Guide

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We describe practical, effective, office-based methods for physicians to use to assist patients to stop smoking that do not require special training or support personnel. Brief counseling achieves smoking cessation in a small percent of well patients but is more effective in patients with smoking-related illnesses or abnormal laboratory test results. Routine prescribing of nicotine gum without participation by the patient in a smoking-cessation program does not increase smoking cessation, and we do not recommend it. The prevention of smoking relapse can probably be enhanced by scheduling follow-up office visits after the patient has quit. Failure to quit on initial attempts should not discourage physicians and patients, since most successful abstainers usually must make several attempts to quit. We outline for physicians two approaches, one brief and one more intensive, to help patients stop smoking.

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Smoking is the principal avoidable cause of death in the United States, with an estimated 315,120 lives lost in this country in 1984 due to this habit.[1] Smoking causes increased mortality not only in the elderly but also in the young, as this habit is responsible for 8.1% of all years of potential life lost in the United States in persons less than 65 years old. A 35-year-old man who lives in the United States and smokes 25 or more cigarettes per day has a 15.6% chance of dying from a smoking-related disease before age 65.[2] Among men in the United States, smoking causes 80% of laryngeal and lung cancers, 85% of cases of chronic obstructive lung disease, and a large proportion of several other serious neoplastic, circulatory, digestive, and respiratory conditions.[1] A smoker's habit also exposes nonsmokers to health risks. The US Surgeon General recently concluded that passive smoking causes lung cancer in nonsmokers and more frequent respiratory tract infections and symptoms in children of smoking parents.[3]

Smoking cessation has been shown to lead to declines in the rates of coronary heart disease, chronic obstructive lung disease, and cancer deaths, thereby providing the rationale for physicians to encourage discontinuation of this habit among their patients. Epidemiologic studies of former smokers have shown that after five to nine years of cessation, coronary heart disease deaths and mortality from all causes were 25% and 18% lower, respectively, as compared with rates for current smokers.[4] After 15 years of cessation, the death rate from bronchitis and emphysema among former smokers was 25% to 50% that among current smokers.[5,6] After ten or more years of cessation, the death rate from lung cancer among men who formerly smoked 20 or more cigarettes per day was 20% of that of men currently smoking this amount.[7]

Because many of the adverse effects of smoking are reversible to a large extent, physicians will ensure improved future and possibly present health for patients whom they help quit this habit. Physicians have the potential to reach a large segment of the US population, since it is estimated that about 70% of US residents see a physician yearly.[8] The public health impact of reducing smoking among the 38 million adults in the United States who smoke and see a physician yearly would be enormous, even if only 5% to 10% of these persons quit on a long-term basis because of physician intervention.

Unfortunately, the great potential for physicians to intervene in the smoking cessation process has not been realized. Medical records rarely identify patients as smokers unless a smoking-related diagnosis is present.[9] Less than half of persons seeing a physician in the past year recall any message from the physician about stopping smoking.[10] Physicians seem to concentrate smoking cessation efforts on those patients who already have an illness related to their smoking habit instead of practicing primary prevention on healthy smokers.[11,12] Perhaps this is due to the disease orientation of most practicing physicians.

Although most physicians recognize the importance of smoking as a risk factor for disease, they think that their influence on the smoking habits of their patients is small.[13] The frustration felt by many physicians may stem in part from unrealistic expectations of success. Even intensive smoking cessation programs using a variety of behavioral and pharmacologic approaches rarely obtain more than a 40% long-term quit rate.[14] Physicians' disappointment with the 5% to 10% cessation rates they achieve is inappropriate because those rates extrapolated to the US population would result in several million more ex-smokers each year.

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We present a practical plan for physicians to use to help their patients quit smoking based on our critical review of the current literature. We limited our review of available strategies for cessation to controlled trials of interventions conducted in a practice setting. This criterion led to the exclusion of many smoking cessation methods that had not been subjected to rigorous evaluation using appropriate controls and adequate follow-up. We avoid extensive discussion of methods unsuitable for use in a physician's office or requiring special training, such as aversive conditioning, acupuncture, or hypnosis, and refer interested readers to the review by Schwartz.[14] Instead, we describe those techniques that any physician can use during a busy work day to help patients quit smoking. Many techniques have been reported that meet these criteria, but we have weeded out those of dubious merit. We also provide addresses for free smoking cessation materials and recommend routes of referral should initial efforts fail to achieve the desired end.

TABLE 1.—*Brief Physician Intervention to Achieve Smoking Cessation*

- Identify all smokers
  - Elicit a smoking history
  - Record "tobacco dependence" on the problem list
  - Ask about smoking at each visit
  - Ask smokers if they want to quit and whether they are ready to quit now
- Brief cessation advice
  - Give all smokers a strong message that smoking is harmful to their health and that they should quit now
  - Describe the main risks of smoking; focus on risks that are relevant to current patient complaints rather than long-term dangers
  - Avoid high fear messages; emphasize the positive benefits of cessation
  - Tell all smokers in clear and unambiguous language that they should quit, whether or not they are ready to quit now
- Self-help programs—for patients who are interested in quitting
- Relapse prevention
  - Enlist spousal support
  - Counsel to avoid situations where relapse is likely
  - Boost patient confidence in the ability to quit
- Follow-up contacts—for patients who decide to quit

Physician's Role in Smoking Cessation

A physician's role in counseling patients to quit smoking consists of five components, as described below and briefly outlined in Table 1.

Identifying the Smoking Habit

Physician counseling on stopping smoking begins with the identification of smokers. A survey by Fortmann and colleagues indicated that 90% of physicians in Monterey County, California, asked about smoking in patients with cardiovascular or respiratory symptoms, but only 70% asked routinely.[11] Because any targeted intervention depends on knowing who the smokers are, asking about smoking habits at the initial visit should be a routine procedure. It is important to ask about the duration of smoking, amount smoked, and brand smoked. Those patients who report an inability to quit, the development of withdrawal symptoms, or who persist in smoking despite a tobacco-related medical condition suffer from tobacco dependence.[15] Physicians should make the diagnosis of tobacco dependence in all such smokers. Simply recording that smoking is a health problem in the

TABLE 2.—*Controlled Trials of Physicians' Advice on Smoking Cessation*

Study	*Type of Practice*	*Patients, No.*	*Interventions*	*Follow-up, months*	*Quit Rate, %*
Mausner et al, 1968[27]	General	157	None	6	0.0
			Advice		5.0
Russell et al, 1979[18]	General	2,138	None	12	0.3
			Questionnaire		1.6
			Brief advice		3.3
			Advice plus booklet plus follow-up		5.1
Wilson et al, 1982[19]	Family	211	Advice	6-12	12.0
			Advice plus follow-up		23.0
Stewart and Rosser, 1982[20]	Family	691	Questionnaire	12	11.7
			Advice		10.5
			Advice plus booklet		12.8
Russell et al, 1983[21]	General	1,938	None	12	6.0
			Advice		6.4
Jamrozik et al, 1984[22]	General	2,110	None	12	10.6
			Advice plus booklet		15.0
			Advice plus booklet plus carbon monoxide measurement		17.2
			Advice plus booklet plus health visitor		13.2
Fagerstrom, 1984[23]	General	151	Advice plus short follow-up	12	3.0
			Advice plus long follow-up		15.0
Li et al, 1984[24]	Prenatal clinic	1,179	Questionnaire	12	0.9
			Advice		3.7
Richmond and Webster, 1985[25]	General	200	Control	6	3.0
			Advice plus risk factors plus follow-up		33.0
Page et al, 1986[26]	General	227	Control	6	8.1
			Advice		8.9
Janz et al, 1987[28]	General medical	250	Control	6	10.0
			Advice		15.0
			Advice plus booklet		20.0
Thompson et al, 1988[29]	Prepaid health plan	953	Control	9	16.0
			Advice		10.0
			Booklet		10.0

medical record and sharing this fact with the patient has been shown to increase both patients' awareness of smoking as a health problem and patients' six-month cessation rates.[16]

We recommend that a patient's smoking status be placed on the problem list and flow sheet. This facilitates following up on smoking habits and documenting interventions. Cohen and co-workers have shown that medical record reminders about eliciting a smoking history and setting a quit date are effective in increasing the frequency and intensity of physician counseling.[17] As a minimum, all physicians should ask about smoking and other tobacco use at a patient's initial visit, note their findings in the medical record, and share the diagnosis of tobacco dependence with the patient.

Brief Counseling

The efficacy of having physicians give patients a simple message pointing out the hazards of smoking and the benefits of cessation has been studied in a number of controlled trials.[18-29] Table 2 shows that trials of brief counseling conducted in medical practices with at least a six-month follow-up have resulted in quit rates between 3% and 20%.

Tailoring of counseling to a patient's clinical condition appears to magnify the effect of physician intervention. The impact of advice is particularly apparent in a patient with a recent myocardial infarction. Burt and associates found that 63% of patients who had had a myocardial infarction and were given brief advice in hospital remained abstinent for one year compared with only 27% in a control group.[30] Using the patient's clinical condition, such as pregnancy, newly diagnosed obstructive lung disease, or claudication, as a springboard for counseling about cessation will increase the effectiveness of a physician's message.[31-33]

Focusing on cardiovascular risk factors or other measurable effects of smoking in high-risk patients greatly increases the cessation rates seen with physicians' advice.[34-39] Data on these risk factor studies are summarized in Table 3. These trials were not carried out in medical clinics, so one must be hesitant in directly extrapolating the data to physician advice in routine patient visits. One study used a discussion of risk factors in a medical setting. Richmond and Webster[25] used pulmonary function testing and carboxyhemoglobin measurement in addition to advice and found a quit rate similar to that of the risk factor trials shown in Table 3. Collecting risk factor data and discussing the beneficial effects of reducing levels of risk factors appear to more than double the success rates of physician counseling on smoking cessation, resulting in long-term quit rates of 18% to 51%. This increased quit rate must be balanced against the increased effort and expense of a program that includes measuring cardiovascular risk factors or the effects of smoking.

We recommend that physicians use easily available tests to personalize the quit-smoking message. Office spirometers are available in many clinics and are particularly useful in smokers with attacks of winter bronchitis or those with dyspnea on exertion. Doing a spirogram and interpreting the results take about five minutes and often make a major impression by showing reduced forced expiratory volumes in one second (FEV_1) in many otherwise asymptomatic smokers. Many smokers are impressed by a calculation of lung age—the age at which a patient's FEV_1 would be normal.[40] The carboxyhemoglobin test is relatively expensive (about $20) and cannot be generally recommended. Measuring expired carbon monoxide levels provides the same information as measuring carboxyhemoglobin and is a simple, noninvasive test. The instrument that measures expired carbon monoxide—such as MiniCo or Vitalograph—is relatively inexpensive (about $800) and yields abnormal values in almost all smokers, even in younger ones with normal results on pulmonary function tests. Thus, one can discuss a concrete abnormality in all smokers and avoid the "My lungs are OK, so I can keep on smoking" attitude sometimes seen when using spirometry as a counseling aid.

A physician should also use cardiac risk factor data to enhance the smoking cessation message. Smokers at high risk for cardiac disease because of hypercholesterolemia, hypertension, diabetes mellitus, or family history are more likely to experience an adverse cardiac event caused by smoking and thus have more to gain from abstaining than if the overall cardiac risk were low.

Self-Help Programs

Many self-help programs have been developed to assist smokers to quit. A list of these can be found in Figure 1. They have a definite role to play because most smokers would rather quit on their own than attend a cessation class.[28,29] A number of recent studies have found increased quit rates ranging from 7% to 37% among persons given self-help programs.[14,41] The effectiveness of such programs in a practice setting has varied.[42-44] Although the effect of self-help materials alone is small, they are an inexpensive alternative to more complex physician intervention and should be routinely available in offices and clinics.[45]

Relapse Prevention

The key to successful smoking cessation is preventing relapse. Many smoking cessation methods achieve initial quit rates of 70% or more,[46(p472)] but within six months, most quitters have resumed smoking. Personal characteristics, such as low anxiety, good personal adjustment, and a low addictive score,[47] have been identified as factors leading to

TABLE 3.—*Physician Counseling and Smoking Cessation in Cardiovascular Risk Factor Studies*

Study	Site	Patients, No.	Intervention	Quit Rate, %
Rose and Hamilton, 1978[35]	Civil service	1,445	Control	10.0
			Determine risk factors plus advice plus follow-up	51.0
Hjermann, 1980[37]	Community	1,232	Control	17.0
			Intervention	25.0
Cambien et al, 1981[36]	Civil service	3,336	Control	14.3
			Intervention	23.1
Werko, 1979[38]	Community	9,998	Control	26.0
			Intervention	31.0
Kornitzer et al, 1980[34]	Factory	1,468	Control	12.5
			Advice plus determine risk factors	18.7

CESSATION GUIDES

The Physician's Guide: How to Help Your Hypertensive Patients Stop Smoking, NIH Publication 83-1271, 1983

Clinical Opportunities for Smoking Intervention: A Guide for the Busy Physician, NIH Publication 86-2178, 1986

Both available from National Heart Lung and Blood Institute, Smoking Education Program, Building 31, 4A-21, 9000 Rockville Pike, Bethesda, MD 20892

SELF-HELP PROGRAMS

"Quit For Good" Kit, National Cancer Institute, Office of Cancer Communications, Building 31, Room 10A18, Bethesda, MD 20892 or call 1-800-4-CANCER. A cessation program for physicians that includes free materials for 50 patients

"Freedom from Smoking in 20 Days" and "A Lifetime of Freedom from Smoking," American Lung Association, 1740 Broadway, New York, NY 10019—or from your local American Lung Association chapter

"I Quit Kit," American Cancer Society, 4 West 35th St, New York, NY 10001, (212) 736-3030—or from your local American Cancer Society chapter

Figure 1.—Some resource materials for smoking cessation.

prolonged cessation. A physician who is not a psychiatrist can probably do little to help patients achieve these personal characteristics.

Most physicians can, however, profitably direct efforts to creating a social structure supportive of nonsmoking. Successful cigarette abstainers more frequently have spouses who are supportive,[48] who are former smokers, or who quit with them.[49] A physician may therefore promote continuing abstinence if a patient's partner is a nonsmoker by instructing the partner to be supportive of the cessation effort by providing compliments and encouragement instead of nagging or criticism, or, if the patient's partner smokes, by persuading the partner to join in quitting, thereby increasing the chances for mutual prolonged abstinence. Although there is no evidence to our knowledge that banning of smoking in public places and the worksite will help the recent former smoker continue to abstain, we think that this is likely to be the case because opportunities for relapse will be less frequent. Efforts by physicians to restrict smoking in public places and the worksite may further assist in creating an atmosphere supporting nonsmoking.

Certain situations are more likely to lead to relapse, and physicians should work with patients to identify these situations. Schiffman, for example, has identified four typical smoking relapse scenarios: social drinking with tobacco smoke exposure, relaxing at home following a meal, anxious situations at work, and feelings of anxiety or depression while home alone.[50] Coping skills will help patients avoid smoking when placed in a relapse situation. The simplest coping skill—avoiding relapse situations—could easily be recommended by a physician as a strategy for a patient to employ. When avoidance is not possible, more complex coping strategies can be used, but these require intervention by therapists[51] and would not, therefore, be a maneuver that most physicians without special training could personally offer patients.

Physician intervention in altering a patient's self-perception may also assist in avoiding a smoking relapse. A patient's expectation of success has been shown to be predictive of a prolonged abstinence from smoking. Two studies found that a positive expectation of quitting smoking was related to successful long-term abstinence.[47,52] Thus, although no clinical trial has been done on this issue, there is reason to think that a physician boosting the confidence of a patient who desires to quit may lead to a higher rate of prolonged abstinence. A physician should also advise the patient not to feel despair at the chances of quitting smoking if relapse occurs, since long-term quitters on average make more than one serious attempt to quit smoking before they are free of their habit.[53]

In summary, physicians can help to prevent relapse by promoting a social milieu conducive to abstinence, by helping patients to identify and cope with relapse situations, and by fostering confidence of patients in their ability to cease smoking, even if previous attempts at abstaining have failed.

Follow-up Appointments

Active follow-up of patients who are making serious attempts to quit smoking also appears to increase the likelihood of success. Studies that included scheduled appointments after the initial counseling session showed quit rates from 5% to 33%.[18,19,23,25] Physicians should use these follow-up conversations to discuss coping with withdrawal symptoms, preventing relapse, and trying to quit again for those who have relapsed.

Brief physician advice will help 5% to 15% of smokers to quit. This effect can be enhanced by adding the other components of our brief intervention plan (Table 1). If this is unsuccessful, physicians can consider referring the patient to a specialized smoking cessation program. Few patients, however—perhaps 5% of all smokers—will avail themselves of formal cessation programs if they are offered.[29] We do not recommend commercial cessation programs, since few have been adequately evaluated.[14] For interested smokers, the local chapters of the American Lung Association or American Cancer Society will be able to provide information on cessation programs in their area. An alternative to referral is to pursue a more intensive intervention with the patient, as we will describe.

Pharmacologic Treatment of Tobacco Dependence

Given the magnitude of the health effects of smoking, why do people persist in smoking? Nicotine dependence is a major factor. Chronic tobacco use in the form of cigarette smoking fulfills the three criteria for dependence or addiction, namely, pleasure or reward provided by the habit, tolerance to the effects of the habit, and withdrawal symptoms caused by stopping the habit.[54] The withdrawal syndrome is an important obstacle to quitting; most smokers find the greatest difficulty with abstinence immediately following cessation when withdrawal symptoms are most pronounced.[55]

A myriad of symptoms have been observed within a day after quitting smoking, including a craving for cigarettes, irritability, anxiety, difficulty concentrating, restlessness, impatience,[56] coughing, chest tightness, constipation, and mouth sores.[57] Most symptoms decrease in intensity over the first seven days, with only a craving for cigarettes noted after three weeks of abstinence. Those who formerly smoked more than 20 cigarettes per day reported more withdrawal symptoms than did lighter smokers,[57] particularly irritability. Smokers who have made previous attempts to quit only to relapse may expect withdrawal symptoms with future at-

tempts at quitting similar to those experienced with previous episodes of abstinence.[58] If physicians anticipate these symptoms and prepare patients for them, then withdrawal symptoms will be less likely to lead to relapse. For example, constipation commonly occurs after quitting, especially in women, and can be controlled by adding fiber to the diet. Also, patients having difficulty in clearing pulmonary secretions in the first weeks of cessation can be treated with the short-term use of bronchodilators.

Effective drug therapy for tobacco withdrawal following smoking cessation has been sought for many years with little success. Nicotine polacrilex gum is the first agent that has been proved to increase quitting rates in smokers by alleviating many of the symptoms of withdrawal.[59] By blocking withdrawal symptoms, the gum can assist in cessation and the prevention of relapse.

Nicotine Gum in Medical Practice

The effectiveness of nicotine gum has been extensively studied in smoking cessation clinics. When combined with psychological and behavioral counseling, it causes a doubling of the cessation rates, with long-term quit rates ranging from 12% to 70%.[60] Highly dependent smokers tend to benefit from using nicotine gum to a greater degree than do smokers with low or moderate dependency.[61] Another consistent finding is that the longer the gum is used, the higher the quit rate.[62]

Unfortunately, the excellent results with nicotine gum found in smoking cessation programs have not carried over into medical practice settings. There are now eight published controlled studies that have examined nicotine gum use as prescribed by physicians (Table 4),[21,23,26,63-67] of which four showed a significant advantage to using nicotine gum. In several of these studies, nicotine gum was given to all smokers, regardless of motivation, which probably lessened its possible benefit. When the gum is given to all smokers, only 54% actually fill the prescription and only 35% use more than two boxes of the gum.[68] Thus, patient motivation may play a crucial role in nicotine gum's efficacy. Many of the studies were limited by a small sample size and showed only a nonsignificant trend favoring the use of nicotine gum. In addition, the intensity of advice on cessation and instruction on using the gum given to patients varied substantially among the studies.

As might be expected from such varying data, overviews of the effectiveness of nicotine gum in clinical practice have given divergent results. Jamrozik and colleagues[64] and Lam and co-workers[60] thought that the gum was efficacious in smoking cessation clinics, but that there was not enough evidence to recommend its use in general practice. On the other hand, Oster and associates[69] carried out a complex analysis based on an assumption that nicotine gum use could increase cessation rates from 4% to 6% and found the use of nicotine gum to be as cost-effective as the treatment of hypertension. They concluded that the routine use of the gum was justified in general practice. Only two of the six studies using nicotine gum combined with brief advice showed a significant benefit, however, and so we think that routine prescribing of nicotine gum with brief advice will not lead to quit rates much higher than those seen with advice alone.

With much more intensive intervention, nicotine gum can be used successfully by physicians. Tonnesen and colleagues carried out two studies in pulmonary clinics[66,67] in which nicotine gum was used in combination with a series of physician-led group sessions. They found high long-term cessation rates—up to 44%—especially in highly dependent smokers. These results show that nicotine gum can have a major influence on smoking cessation if a physician uses it in the same way it is used in a smoking cessation clinic. To do so, a physician must select only motivated patients, assess the nicotine dependence level, carefully instruct the patient on the use of the gum, use behavioral strategies in addition to the drug, and arrange frequent follow-up visits.

As one can see, patients' successful use of nicotine gum would require a major commitment of time on the part of the physician. It should be reserved for carefully selected patients, and, thus, its use is not feasible in most physicians' practices. If a physician can enlist the help of interested health care providers in the office, such as nurses, then the time commitment would be less of a problem, and nicotine gum use would be a more practical therapy.

Many other drugs, ranging from lobeline to clonidine,

TABLE 4.—*Controlled Trials of Nicotine Gum Use in Medical Practice*

Study	*Type of Practice*	*Patients, No.*	*Intervention*	*Quit Rate, %*
British Thoracic Society, 1983[63]	Chest clinics	777	2 mg gum	9.8
			Placebo gum	11.4
Fagerstrom, 1984[23]	General	151	2 mg gum	25.0
			No gum	9.0
Russell et al, 1983[21]	General	1,983	Control	3.9
			Advice plus booklet	4.1
			Advice plus 2 mg gum	8.8
Jamrozik et al, 1984[64]	General	200	2 mg gum	10.0
			Placebo gum	8.0
Page et al, 1986[26]	Family	289	Advice	8.9
			No advice	8.1
			Advice plus 2 mg gum	12.0
Shaughnessy et al, 1987[65]	Family	99	2 mg gum	12.2
			2 mg gum plus instruction	10.0
Tonnesen et al, 1988[66]	Chest clinics	172	Control	3.7
			2 mg gum	27.0
			4 mg gum	27.0
Tonnesen et al, 1988[67]	General	173	Placebo gum—low dependence	22.6
			2 mg gum—low dependence	38.3
			2 mg gum—high dependence	12.1
			4 mg gum—high dependence	44.4

have been tested to assist in smoking cessation. None have proved to result in long-term cessation. The use of clonidine[70] is under active study because of its effect in diminishing the craving for cigarettes during cessation, but its use must still be considered investigational until more data are available.

Intensive Practice-Based Intervention

An intensive behavioral program using nicotine gum requires motivation and commitment on the part of physicians and patients. Most studies show that the more effort a physician expends on smoking cessation, the greater the quit rate obtained. Physicians should consider an intensive intervention only after having experience and success with the brief intervention. We describe here an intensive smoking cessation program using nicotine gum that is implemented along with the brief program shown in Table 1.

Identify the Smoking Habit

• Judge the patient's motivation to quit. Ask about previous attempts to quit, withdrawal symptoms, and recent brand switches. A person who has switched from a high-tar to a low-tar cigarette has shown some motivation to change behavior. Ask why the patient wants to quit. Answers that reflect a personal motivation ("I am short of breath") are signs of greater motivation than are those reflecting external pressures ("My wife wants me to quit" or "I know it is bad for my health"). Ask patients how ready they are to quit now and how likely it is that they will succeed. Patients who report they are very ready and who feel they can quit are more likely to do so.[71]

• Assess the level of tobacco dependence. Three questions taken from the Fagerstrom questionnaire[72] can identify a highly dependent smoker: number of cigarettes per day (> 25 = high dependence); time to first cigarette (those subjects who smoke within 30 minutes of awakening are likely to be highly dependent); and cigarette brand (high tar and nicotine brands usually point to a high dependence). A highly dependent smoker should be considered for a nicotine gum trial.

• Assess the risk of smoking to the patient. The simplest approach is to test pulmonary function in the office and calculate the lung age. Other possibilities include measuring expired carbon monoxide levels and assessing cardiac risk factors.

• Based on the information from these assessments, divide the patients into groups. In those who are not motivated to quit, ask about smoking at each visit, use teaching moments to reinforce the cessation message, and identify barriers to quitting. At a later date, they may become motivated to quit. In the motivated group, move on to creating a cessation plan.

Create a Behavioral Smoking Cessation Plan

Have the patient set a quit date and keep a smoking diary for several days, listing the time, circumstances, and mood when each cigarette was smoked. Review the smoking diary at the next visit. Identify smoking situations and discuss with the patient some alternative behaviors for those settings. For example, suggest that the patient spend coffee breaks chewing gum with nonsmoking co-workers and avoid smokers during these times. Discuss the patient's previous attempts to quit and anticipate problems of withdrawal and relapse. The patient should be encouraged to use a self-help program.

TABLE 5.—*Instructions on the Proper Use of Nicotine Gum*

Most patients require between 7 and 15 pieces per day
Taper down to 20 cigarettes a day before trying the gum
Do not start to use the gum until you have stopped smoking completely
Do not drink coffee or other beverages immediately before or while chewing the gum
Chew the gum slowly—each piece should last about 30 minutes
Chew until you feel a tingling, then stop; start again when the tingling goes away
Carry the gum with you all the time
Start chewing before you get into a relapse situation
Avoid swallowing the saliva generated by chewing (it contains the nicotine)
Use the gum for at least 3 months before starting to taper
When you first quit, chew at least 1 piece an hour, whether or not you feel withdrawal symptoms

Maintain Abstinence Through Follow-up

Arrange to contact the smoker just after the quit day either in the office or by phone. If the smoker has quit, encourage this and focus on problems of withdrawal and relapse. If he or she did not, try to set another quit date and focus on the problems to be overcome to achieve this goal. Schedule at least one more visit specifically to discuss maintaining abstinence.

Use Nicotine Gum in Motivated, Tobacco-Dependent Patients

Emphasize that patient must quit completely before using the gum. Have a heavy smoker (> 40 cigarettes per day) taper down to 20 cigarettes per day before quitting. Give patients a sample of gum and show them how to use it (Table 5).

Conclusions

Many strategies have been developed to promote smoking cessation. Not all of these are feasible for implementation by practicing physicians. The brief intervention strategy we describe can be used by physicians to assist smokers in quitting. It takes only a few minutes and can lead to cessation rates of between 5% and 15%.

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Specialty Conference

Beyond the Physicians' Reference
The Ethics of Active Euthanasia

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Associate Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

ALBERT R. JONSEN, PhD*: "It's Over, Debbie," a short essay published in *The Journal of the American Medical Association,* has stimulated a vigorous debate over physicians' participation in mercy killing.[1] The debate is not new: the issue has nagged at medicine for centuries.[2] In recent years in the United States, however, it has become somewhat more intense. The effective liberalization of the law against euthanasia in the Netherlands was publicized on a popular American television news magazine. A teledrama fictionalized an actual case of mercy killing. An attempt was made to qualify for the ballot a proeuthanasia statute in California. The shocking, yet poignant words of "It's Over, Debbie" were the spark to this smoldering interest in euthanasia. Should a physician kill a suffering, incurably ill patient?

The classic arguments against mercy killing are quickly rehearsed.[3] First, a prohibition against the direct taking of human life, except in self-defense or the defense of others, has been a central tenet of the Judeo-Christian tradition. Second, the ethics of medicine has always emphasized the restoration of health and has long repudiated killing the sick. The Hippocratic Oath states, "I will not administer poison to anyone where asked to do so nor suggest such a course." Third, the dedication of the medical profession to the welfare of patients and to promoting their health might be compromised by the complicity of physicians in the death of the very ill. Fourth, the slippery slope always threatens: an "angel of mercy" can become a fanatic, bringing the "comfort of death" to those who do not clearly request it, then to others who "would be better off dead," and finally to whole classes of "undesirable" persons. The "euthanasia" program initiated in Germany in the 1930s was first directed only to the incurably ill; it gradually expanded into genocide.[4]

These classic arguments persuade many that physicians have an absolute obligation to refrain from active euthanasia; others are not so convinced. Some physicians are sympathetic toward active euthanasia and admit (privately to colleagues or anonymously in surveys) that they have practiced it. The Hemlock Society has reported that it destroyed questionnaires in which 118 physicians out of 588 questioned admitted they had committed the mercy killing of a patient (*New York Times,* February 25, 1988). Many philosophers are skeptical of the classic arguments. They question their logic and the intelligibility of the major terms and distinctions, such as "killing" versus "allowing to die," "direct" versus "indirect" killing, "active" versus "passive," "ordinary" versus "extraordinary," "omission" versus "commission." Indeed, one such challenge by philosopher James Rachels was published in *The New England Journal of Medicine* several years ago.[5] The somewhat cerebral argument of that essay, which logically concluded that active euthanasia was ethically acceptable, stirred up nothing like the storm of protest that the vivid story of Debbie's death aroused. Adding insult to injury, even the historians cast doubt on the meaning and observance of the venerable Hippocratic injunction.[6] Finally, proponents of legalizing euthanasia assert that sufficient barriers of law and policy can be built to prevent a slide down the slippery slope.

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (1978-1983) examined carefully the classic arguments about euthanasia. In general, the commission shared the skepticism of its resident philosophers' analyses of these arguments. It did not commend their use as the basis for ethical decision making. At the same time, it recognized that the classic arguments and distinctions are not without utility:

> The distinction between acting and omitting to act provides a useful rule-of-thumb by separating cases that probably deserve more scrutiny from those not likely to need it . . . the commonly accepted prohibition of active killing helps produce the correct decision in the great majority of cases . . . thus the Commission concludes that the current interpretation of the legal prohibition against active killing should be sustained.[7]

The renewed debate over active euthanasia comes at a crucial time in the history of medical ethics in America. The broad discussions about foregoing life-supporting and life-extending treatment have led to a consensus within the profession and the public that certain treatments may ethically be omitted by a physician, patient, and family, even if death ensues.[8] The ethics of "orders not to resuscitate"—decisions not to initiate critical care and to discontinue such care once begun—have reached wide acceptance. Debate continues at the margins about such issues as discontinuing nutrition or hydration. This has been a reasonable and beneficial re-

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sponse to the exaggerated use of technology and to the deplorable neglect of patients' preferences.

Now, however, the premonitions of some critics of these developments seem to have come true: if we permit the omission of treatment, they warned, we will soon tolerate the commission of lethal acts. If the strong injunction to save and prolong life is relaxed even in the least, the stronger prohibition against killing will begin to weaken. So, despite the commission's endorsement of the legal prohibition against active killing, the words of the philosopher Rachels may become the common wisdom: "If my contention is right, it follows that active euthanasia is not any worse than passive euthanasia . . . and the difference in some cases in their consequences . . . may make active euthanasia, and not passive euthanasia, the morally preferable option."[5]

Thus, in only a few years, the debate over euthanasia has moved from the acceptance of foregoing life support to the serious consideration of lethal acts. In the face of this apparent confirmation that we are starting down the slippery slope, many physicians may begin to worry. Most physicians, it seems, find mercy killing repugnant. Yet, if the classic arguments are philosophically and historically indefensible, how can that repugnance be rationally justified? What "arguments for the faith that is in them" can those physicians who are reluctant to become accomplices in mercy killing offer? The President's commission urges, "Health care professionals, individually and through their professional associations, must become more active in creating, explaining, and justifying their standards regarding appropriate professional roles."[7] Yet, if the classic arguments seem so unconvincing to the ethicists, how can health care professionals accomplish this task?

The words "appropriate professional role" provide a clue. It can be postulated that killing is none of a physician's business. The business or appropriate professional role of a physician is to use scientific knowledge and clinical experience in making decisions and advising patients about the prevention, diagnosis, and treatment of disease and the maintenance of health. Being a physician in this modern era of medicine means having been educated and trained in just these skills; being a good physician means having the competence to perform them well; being a poor physician means doing them poorly. In addition to this scientific and clinical competence, a good physician possesses some "virtues," such as respect and compassion, caution and courage, that make clinical competence the basis for a humane relationship with patients.[9]

Killing a human being requires none of these skills or virtues—except, perhaps, caution and courage. It is an act requiring only the most rudimentary knowledge about the vulnerability of the human body. Although there are professional killers of considerable skill, and killing can be made more efficient by training, it is essentially an untutored activity, performable by any person strong enough to wield a club, steady enough to shoot straight, or smart enough to know arsenic from sugar. Killing can be done in a blind rage or by an insane or inattentive person. A killer may feel no compunction or be consumed by guilt. In other words, killing a human being is a vulgar activity, an ordinary sort of human act.

There is no reason why physicians as such should have any particular role to play in this tragically ordinary activity. The knowledge and competence whereby they are designated as physicians are irrelevant to killing. Indeed, their knowledge of physiology and of pharmacology may make their killing more efficient than that of amateurs, but that does little to recommend it as part of their business. In recent years, technicians have been trained to deliver lethal drugs to condemned criminals. Anyone who has a skill can put it to an inappropriate use: a butcher may commit efficient mayhem, a locksmith can be an accomplished burglar.

This line of argument will seem to some a mere tirade against physicians' involvement in active euthanasia. They expect a logically impeccable argument that either works down from some manifest principle or works out to inconvenient consequences. There are many essays that do just this, some brilliantly.[10,11] Instead, I have proposed that "being a physician" and "killing a patient" have nothing to do with each other. I consider this a proper ethical argument. Ethical arguments are not devised solely of theories, principles, and the logic of reasoning. They rest also on cultural and social conceptions of the roles persons live out and the responsibilities and expectations attached to those roles in particular times and places. The physicians' role, both stable and changeable in our history, is as much the basis of our understanding of moral obligation as is the universal principle of, say, benevolence or nonmalevolence. The principles, so abstract in themselves, must be attached to the history, traditions, social needs and expectations, and even cultural myths that surround particular roles. These, as well as the principles, go toward defining the moral responsibilities of physicians. Active euthanasia, we contend, lies outside those responsibilities.[12]

I am repeating in my own way the remarks of Lord Horder arguing in the House of Lords in 1936 against the Voluntary Euthanasia bill: Most doctors, he said, were sympathetic toward the modern efforts to secure biological control before life began and while it lasted. But in the matter of putting an end to life, surely a new principle entered and that principle was outside the doctor's reference.[13]

"Outside the doctor's reference" is a fine phrase, although a somewhat careless one: a physician's training, knowledge, and skill do encompass a principle that governs putting an end to life. That principle—that "there is no obligation to do what is useless or futile"[14]—governs the decision to forego useless or futile treatment. Its application depends precisely on the competent medical judgment, based on science and clinical experience, that a treatment is highly unlikely to attain the goal of restored health. (Physicians are also bound by another principle—respect for the autonomy of the patient—but its application does not depend on a physician's skills. At the same time, neither does its application extend to acceding to a request that the physician do something that lies outside the bounds of his or her responsibility.)

The killing of a patient by lethal injection, however, is beyond the physicians' reference. It is not an act of *medical* skill, although a "grim prognosis" is a proper medical determination and the lethal act itself might be medically informed by a knowledge of drug dosage. But the principle "in the matter of ending life" in this manner is quite different from the principle that governs the foregoing of treatment. That principle is proper to physicians' role in which scientific and clinical judgment defines one's moral as well as technical tasks. It dictates that, at a certain time in the course of care, therapeutic measures are no longer beneficial. But this "new" principle addresses the different question of whether

one person might attack another with lethal intent. This is not, of course, a new principle in the sense that it has never before been considered. Ethical reflection on the problem of killing has a long history. It is a new principle in the sense that it is posed as a physician's principle. The long history reflecting on killing contains analogous questions about whether certain roles justify killing: Should a judge condemn a criminal to death? May a cleric kill an attacker in self-defense? Should soldiers kill in defense of their lives? of their king? of their country? Should a husband kill his adulterous wife? In answering these old questions, the role of the person who commits the lethal act is important in deciding whether it is justified or not. We must now ask whether being a physician entitles a person to end the life of another when none of the skills whereby the physicians' role is defined are brought to bear—except the incidental skill of knowing something about drugs.

Those favoring active euthanasia presuppose that being a physician somehow does justify such an act. The proposals for legalizing mercy killings all make physicians, and physicians only, the legally authorized agents. These bills exempt physicians who administer a lethal agent and their consultants from the usual penalties of law on the condition that they follow the correct procedures, namely, diagnosing terminal illness, obtaining the required consultation, and receiving the patient's informed and competent request. Of these procedures, only the first, diagnosing terminal illness, involves a properly medical act.

The new question, then, in the old history of the ethics of killing is why the ability to diagnose a terminal illness—an ability that is, in fact, notoriously fallible—and to prescribe the proper dosage of an appropriate drug (also fallible) justifies the actual administering of that drug. Or, put more plainly, why does medical competence justify an attack with lethal intent? It might be said that one of the major virtues of physicians is compassion, and one of the central tasks is the relief of pain. Does not mercy killing exemplify that virtue and that task? Compassion is, indeed, a commendable virtue, but, as Aristotle remarked long ago, virtue is a mean between opposite vices: compassion is bracketed by pitilessness that ignores another's distress and softheartedness that gushes pity when other remedies might serve better. Compassion can easily slide in the direction of softheartedness and must be held to the mean by a clear sense of purpose and role. Compassionate judges, police, and generals are praiseworthy only when their compassion does not subvert their publicly appointed duty. A compassionate physician exercises that virtue within the limits of the scientific and clinical competence that defines the role. Thus, compassionate competence will discern that a patient is beyond the help of therapy and will manage the patient's pain skillfully and attentively. Compassion that manages pain by destroying the sufferer represents the kind of final solution that solves the "Jewish problem" by genocide or the "black problem" by expelling Zulus into desolate "homelands."

The mere fact of being a physician seems irrelevant to the commission of homicide. Neither the scientific competence nor the virtue of compassion that define the physicians' role provides justification. A physician might step out of the role and act simply as a friend; in so doing, however, he or she becomes like all other humans who kill, subject to the demand that the dreadful act be publicly justified. This defense can sometimes be made convincingly and will be heard sympathetically by judges and juries. It should not be circumvented by endorsing a public policy based falsely on the assumption that certain killings are "medically indicated" and properly done by medically competent persons. Killing, whether done by police, innocent victims of assault, marauders, or physicians, involves a principle beyond the physicians' reference.

The philosophers have, of course, taken note of arguments like the one I offer here and do not find them any more convincing than the classic distinctions. Rachels makes short shrift of the claim that physicians have an obligation not to kill simply in virtue of being physicians by invoking a parallel argument: it would not be right for a mechanic to destroy an automobile because it is the function of mechanics to repair cars. This is, he says rightly, "a silly argument."[15(p120)] I am suggesting, however, that the two arguments are not quite parallel—and not merely because there is "no sanctity of automotive life." I am arguing that being a physician is not, in itself, a role that contains any feature that should exempt physicians from the judgments, sanctions, and blames that fall on any human being who kills another. Killing out of mercy may be excusable or even justifiable killing, but it is irrelevant whether it is done by husband, father, or physician. Every human who kills another stands equally before the judgment of society and of the law; no public policy should carve out a special role for those who are physicians. The principle that governs our moral judgments about killing is a principle that covers all persons and is, as such, beyond the physicians' reference.

Of course, it is not impossible that a new task could be added to those already comprised in the physicians' role. Grocers take on the job of selling lottery tickets; realtors become notaries. Still, "putting away" one's patient may be more than an added task. It would seem a radical revision of the role as it has been understood for centuries. It is a revision that strikes deeply into the heart of the motives and emotions of most contemporary physicians and medical students. Either performing a mercy killing or declining to do so could be equally traumatic (we should recall the trauma that even those now licensed to kill, such as peace officers, report about killing in the line of duty). Also, the added task comes with heavy requirements—the physician must know the patient, understand the illness, and feel sincere compassion; yet, these requirements are added at a time when medicine seems to move inexorably toward the impersonal and bureaucratic. This one added task, voluntary though it be, could change the role and the profession beyond recognition.

"It's Over, Debbie" is a vivid example of our argument. Almost every feature of Debbie's killing was beyond the physician's reference. Debbie was previously unknown to the resident—she was some other physician's patient. Indeed, far from exhibiting the compassion of a friend, the exhausted resident saw the sufferer as a burden. The resident made no use of diagnostic, prognostic, therapeutic, or palliative skills—even the morphine dosage was more a guess than a judgment. What the resident did, any other adult human could have done, if not with morphine, then with a club or a gun. No peculiarly medical act was performed. What the resident might have done as a physician, had he or she so acted, would have been to ascertain with great care Debbie's medical condition, judge the suitability of any change of regimen, and make the fine judgments needed to assuage pain even at the risk of hastening death. All this would have been

within the physician's reference. As told, the story merely relates a case of murder, not of mercy killing. Murder is not a physician's business.

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Book Review

The Western Journal of Medicine does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.

Community-Oriented Primary Care: From Principle to Practice

Edited by Paul A. Nutting, MD. US Department of Health and Human Services, Superintendent of Documents, US Government Printing Office, Washington, DC 20402, 1987. 539 pages, $16 (paperback).

At the time this book was written, Dr Nutting, the editor, was the Director of the Office of Primary Care Studies within the Health Resources and Service Administration of the Department of Health and Human Services. From this office, he was able to stimulate conferences, discussions, and papers regarding how primary care health services could be better directed toward the health needs of the communities that they serve. This book is essentially an anthology of short articles regarding how the concepts of epidemiology or community medicine can be incorporated into the practice of primary care medicine.

Community-oriented primary care is defined by the editor and several of the authors in this book as a synthesis of the traditional practice of primary care medicine with the disciplines of public health, community medicine, or epidemiology. It is an exciting and logical expansion of the primary care movement that has occurred within the United Sates during the past 20 years. The resurgence and the interest nationally in the development of family medicine, general internal medicine, and general pediatrics is evidenced by the growth in the number of residency training programs and the continued demand for primary care physicians in the face of a perceived oversupply of physicians in general. These primary care disciplines have all had a voiced interest in preventive medicine and community medicine but have generally lacked the skills necessary to apply these principles to their primary care practices. Although admittedly in its infancy stage, the community-oriented primary care movement within the US offers not only an orientation to community health problems but some methodologies for inclusion into the practice of primary care medicine.

The book is honest in its description of the problems related to expanding primary care into a community orientation—such problems as our current reimbursement system for health services, the difficulty of defining the community of service, and the denominator of this service population to be studied. It also presents a number of concrete examples of how community-oriented primary care has been successfully incorporated into various practice settings, including the private practice office, group and health maintenance organization practices, and more traditional public health services. Many of the articles describe methodology that would be very helpful to the practitioner considering trying out community health studies, even on a small scale.

Perhaps most important for the practicing physician is an understanding of the limitations presented by the traditional individual care model that typifies most of primary care medicine. This book offers the opportunity to expand the horizons of practice challenges, including understanding the practice population, being able to identify particular health problems within the population served, and supplies mechanisms of evaluating whether interventions by a physician are of any value.

As might be expected from such a compilation of individual articles involving some 76 different authors, the quality of the work is somewhat variable. Dr Nutting does an excellent job, however, in organizing the articles into a logical and helpful progression of understanding community-oriented primary care, the tools necessary for implementing it, some examples of successful programs, and a discussion on the problems of evaluation of such efforts. There are several excellent chapters toward the end, including a wonderful one on the data resources available from the federal government and an annotated bibliography.

I think this book should be a must reading for any primary care physician. Whether or not the physician chooses to attempt any community-oriented primary care activities in his or her practice, the understanding of the concept and how it is being developed across the country would be exceedingly valuable to the practitioner. It is generally well-written, easy to read, and lends itself to selected reading of those chapters or articles that may be of particular interest. I strongly recommend this book.

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Medical Staff Conference

Idiopathic Pulmonary Fibrosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Pulmonologists share a sense that we are on the threshold of a breakthrough in our understanding and treatment of idiopathic pulmonary fibrosis. The development of bronchoalveolar lavage has made the alveolar space seem accessible to direct examination, and the advances in cell biology and immunology seem to promise the means to identify the causes of the hypercellularity and fibrosis that characterize the lungs of patients with this condition. We are pleased to have Marvin Schwarz tell us the clinical characteristics of idiopathic pulmonary fibrosis and the reasons for the continuing optimism that new and effective therapy may someday be available.*

MARVIN I. SCHWARZ, MD†: Although idiopathic pulmonary fibrosis (IPF) has characteristic clinical, radiographic, physiologic, and pathologic features, it remains a diagnosis of exclusion. IPF represents one of the interstitial lung diseases (Table 1). Typically, patients with this disorder have dyspnea, show lower zone diffuse interstitial infiltrates on a chest radiograph, have restrictive physiologic findings with a reduced diffusing capacity for carbon monoxide, and have resting and exercise hypoxemia. A lung biopsy specimen shows varying degrees of inflammation and fibrosis. The first description of this disorder is attributed to Hamman and Rich, who in 1933 reported the cases of several patients with progressive dyspnea and pulmonary infiltrates who died within six months of becoming ill.[1] The mean survival is now estimated to be from four to six years. The rapid downhill course noted by Hamman and Rich is infrequently seen, but rapid deterioration during the clinical course does sometimes occur, more commonly in patients with associated connective tissue disease.

Histopathology

The salient pathologic features of IPF are, first, inflammatory cell infiltration of the distal air spaces followed by collagen proliferation and fibrosis. I should point out that the inflammation-fibrosis pattern is a continuum and areas of end-stage fibrosis and of active inflammation may be found in the same lung. It has been well shown that it is the inflammatory component of the disease that is responsive to therapy.[2]

The initiating agent, whether it be blood-borne or inhaled, remains unknown, but the critical injury is to type I alveolar lining cells. This results in an outpouring into the alveolar spaces of alveolar macrophages along with smaller numbers of neutrophils, lymphocytes, and plasma cells (Figure 1). The interstitium of the lung becomes edematous and is also infiltrated by the aforementioned immune-effector inflammatory cells. These characteristics are thought to represent the early inflammatory phase of IPF and have been described as desquamative interstitial pneumonitis.[3] While it is not unusual to see this histologic stage of disease in any specimen of lung biopsy in these cases, it rarely represents an isolated finding. As the disease progresses, the intra-alveolar inflammation subsides and the inflammatory process becomes more evident within the interstitium. Both lymphocytes and plasma cells infiltrate these structures, and early fibroblastic proliferation is detected. During this phase, known as usual interstitial pneumonitis, hyperplasia of the alveolar type II cell occurs, producing a "hobnailed" appearance of the alveolar walls. The alveolar type II cell is responsible for the repair of the alveolar epithelial cell surface because it has the ability to differentiate into type I cells. As the usual interstitial pneumonitis phase continues, collagen deposition supervenes causing pronounced thickening of the alveolar walls and obliteration of alveolar capillaries. In this advanced phase of pneumonitis, inflammation subsides and medial hypertrophy develops in pulmonary arteriolar walls, presumably in response to hypoxia from the ventilation-perfusion imbalances caused by the inflammatory-fibrotic process. With further fibrosis and derangement of the distal architecture of the lung, honeycombing appears (Figure 2). Here the distal airways appear as cystic spaces lined by metaplastic cuboidal epithelium. Gas exchange in these honeycombed areas is virtually nil. These cystic honeycombed spaces are felt to have the potential to undergo malignant change—adenocarcinoma or alveolar cell carcinoma.[4] Another feature of end-stage IPF is smooth muscle proliferation within the alveolar structures.

Although the interstitial lung diseases, including IPF, are primarily thought of as inflammatory diseases of the distal alveolar units, both the alveolar ducts and respiratory and terminal bronchioles may also be involved, particularly in IPF. Early on, the bronchiolar walls become infiltrated with mononuclear cells, and acute inflammatory cells appear within small airway lumens. New fibrous connective tissue originating from the bronchial lumens extends into the respiratory and alveolar ducts (Figure 3).[5] With time, intraluminal fibrous polyps are formed, and the lesions become

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ABBREVIATIONS USED IN TEXT

BAL = bronchoalveolar lavage
CRP = clinical-radiographic-physiologic
CT = computed tomographic
IPF = idiopathic pulmonary fibrosis

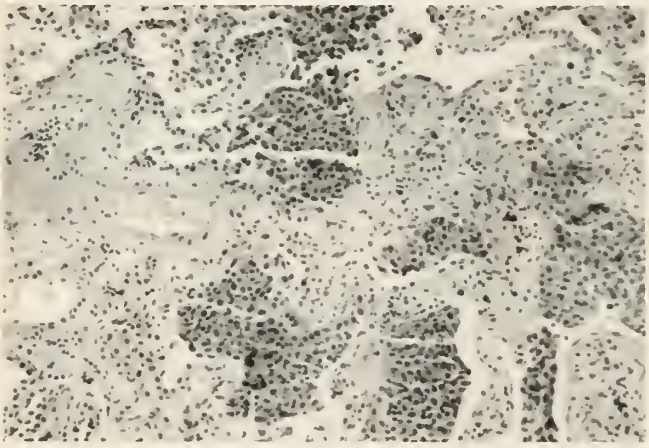

Figure 1.—The photomicrograph shows the inflammatory component of idiopathic pulmonary fibrosis. Note the intra-alveolar macrophage collections and the edema and lymphoplasmacytic infiltrate of the alveolar walls (hematoxylin-eosin stain).

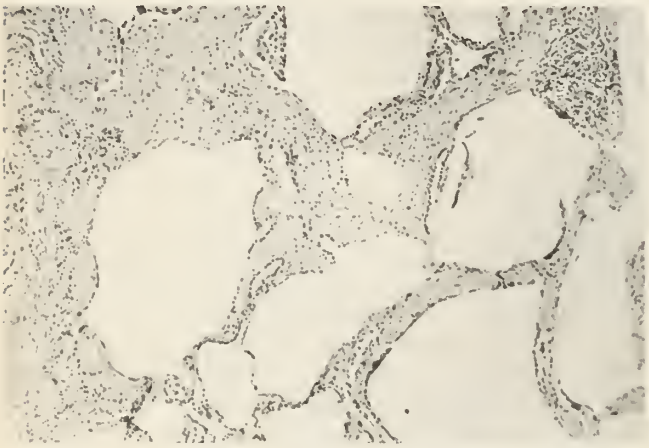

Figure 2.—The photomicrograph shows a specimen of lung with end-stage honeycombing (hematoxylin-eosin stain).

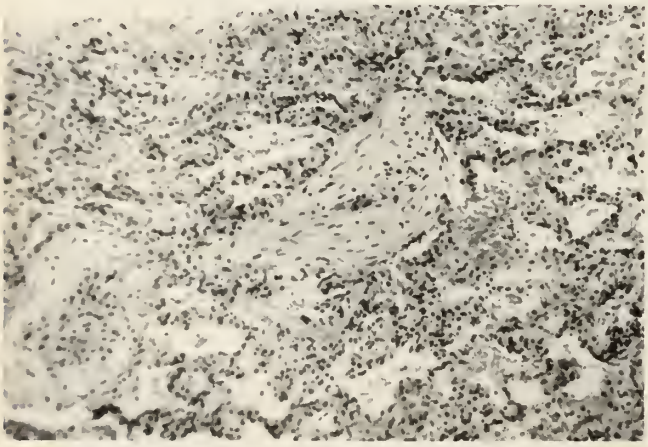

Figure 3.—The photomicrograph shows a cellular (usual interstitial pneumonitis) idiopathic pulmonary fibrosis. In addition, note the intraluminal connective tissue extending from a respiratory bronchiole into an alveolar duct (hematoxylin-eosin stain).

characteristic of bronchiolitis obliterans. While these inflammatory changes in small airways often coexist with the more typical desquamative and early usual interstitial pneumonitis lesions, they may be the sole finding in patients suspected of having an interstitial lung disease. The difference from IPF is that the lesions are bronchocentric and involve only the most proximal alveolar structures. This pathologic process has been called bronchiolitis obliterans with organizing pneumonia.[6] How this isolated lesion fits in the evolution of IPF is unknown. In patients originally diagnosed as having bronchiolitis obliterans with organizing pneumonia and who went on to die, autopsies revealed typical end-stage IPF.[7] In addition, pathologic changes like those of bronchiolitis obliterans may be found with other interstitial lung diseases, such as hypersensitivity pneumonitis, eosinophilic pneumonia, and the interstitial lung disease associated with connective tissue disease.

The other variant of idiopathic pulmonary fibrosis that has a similar clinical-physiologic presentation but more uniform inflammatory pathologic features is lymphocytic interstitial pneumonia. Here the inflammatory infiltrate consists of homogeneous sheets of lymphoplasmacytoid cells that expand the alveolar structures. This process may evolve into pulmonary lymphoma or result in end-stage IPF.[8]

Pathogenesis

Several lines of evidence favor an immunopathogenesis for IPF. First, an identical clinical-histologic sequence occurs with the connective tissue diseases. In addition, inflammatory fibrotic lung disease identical to IPF is associated with a number of other autoimmune conditions including inflammatory bowel disease, chronic hepatitis, idiopathic thrombocytopenic purpura, and essential cryoglobulinemia. Table 2 lists the autoimmune constituents found in the serum of patients with IPF.[9,10] Immune complexes have also been found in both the bronchoalveolar lavage fluid and in the lungs of these patients.[11] The disease has also been produced in animals by instilling either preformed immune complexes or activated fragments of complement as initiating agents.[12]

The cause of the fibroblastic proliferation and collagen

TABLE 1.—*Diagnostic Classification of the Interstitial Lung Diseases*

Drug induced—furantoin, amiodarone, gold, cytotoxic drugs
Pneumoconiosis—asbestosis, silicosis, berylliosis, and others
Connective tissue diseases associated
Primary lung diseases—sarcoidosis, hypersensitivity pneumonitis, eosinophilic granuloma, lymphangitic carcinomatosis, and others
Alveolar filling disorders—alveolar proteinosis, Goodpasture's syndrome, idiopathic hemosiderosis, alveolar sarcoidosis, eosinophilic pneumonia
Idiopathic pulmonary fibrosis and variants—lymphocytic interstitial pneumonia and bronchiolitis obliterans with organizing pneumonia

TABLE 2.—*Autoimmune Constituents of Serum in Patients With Idiopathic Pulmonary Fibrosis*

Rheumatoid factors
Antinuclear factors
Cryoglobulins
Increased immunoglobulins
Immune complexes
Sensitized T lymphocytes (type I collagen)

deposition is unknown. Three distinct possibilities exist: fibroblasts could be directly stimulated by the inciting agent and the inflammatory reaction be a secondary bystander response, the injured epithelial cell lining may release effector substances that initiate fibrosis, and the fibrosis may result from the inflammatory or repair process. The bulk of the evidence suggests that the third possibility is most likely.[13] Immune complexes that are found in specimens of serum, bronchoalveolar lavage, and lungs of these patients are capable of activating macrophages and of attracting neutrophils. Neutrophils have the potential to injure lung through the release of destructive connective tissue enzymes and toxic oxygen radicals. Stimulated macrophages secrete growth factors for fibroblasts and fibronectin. Fibronectin facilitates fibroblasts attaching to the extracellular matrix.[14,15] In addition, macrophages release not only monokines that attract neutrophils but also ones that stimulate the proliferation of T and B lymphocytes—the cells primarily found within alveolar walls in idiopathic pulmonary fibrosis. T lymphocytes in turn release various lymphokines that cause macrophage proliferation, fibroblastic chemotaxis, and B-lymphocyte release of immunoglobulin in response to an antigenic stimulus.[16]

Clinical Evaluation

Most patients who have IPF are between the ages of 40 and 60, have dyspnea on presentation, and show abnormal chest radiographs and pulmonary function. About 10% of cases, however, are detected from a screening chest radiograph showing interstitial infiltrates in an asymptomatic patient. Conversely, about 10% of symptomatic (dyspneic) patients found to have IPF on lung biopsy have normal radiographs.[17,18] In the first instance, one should not ignore an asymptomatic patient with diffuse interstitial infiltrates because this patient will become symptomatic in several months or years and may by then have progressed to the advanced fibrotic phase, which is often not responsive to treatment. The second instance suggests that we should consider the possibility of IPF or another interstitial lung disease in a patient with dyspnea even when a chest radiograph is normal.

On physical examination there is clubbing of the fingers more often in patients with advanced fibrotic rather than earlier inflammatory disease. Bibasilar crepitant rales are typically heard, and the physical findings of cor pulmonale are present in patients with long-standing pulmonary hypertension. In unusual instances, Raynaud's phenomena, digital vasculitis, a discoid lupus rash, or a distal sensory neuropathy is present. Early on, the chest radiograph in patients with IPF shows bibasilar, usually symmetric, reticulonodular infiltrates. With advancing disease, these infiltrates extend into the mid and upper lung zones. Occasionally, a pure alveolar or mixed interstitial-alveolar bibasilar infiltrate is found, often corresponding to the histologic findings of desquamative or early usual interstitial pneumonitis. With far-advanced disease, a characteristic radiographic finding appears at the lung bases: the small cystic spaces of honeycomb lung. This radiographic finding portends a poor prognosis regardless of therapeutic maneuvers. Other radiographic features of advanced IPF include pulmonary hypertension, spontaneous pneumothorax, and a superimposed alveolar cell scar carcinoma. Pleural involvement is not a feature, as it is in asbestosis, connective tissue-associated interstitial lung disease, lymphangitic carcinomatosis, and some drug-induced interstitial processes. Computed tomographic (CT) scanning using thin-cut sections may have a role in detecting interstitial lung disease in a dyspneic patient with a normal chest radiograph.

When compared with patients who have IPF, patients who have bronchiolitis obliterans with organizing pneumonia have a shorter duration of symptoms—1 to 3 versus 3 to 24 months. They also date the beginning of their dyspnea from an upper respiratory tract infection and have mixed alveolar interstitial infiltrates on a chest radiograph.

Pulmonary Physiologic Testing

Pulmonary function testing indicates the severity of impairment, provides objective documentation of the response to therapy, and often aids in the recognition of IPF and other interstitial lung diseases. Lung volumes are typically reduced (restrictive ventilatory impairment), with preservation of the maximal expiratory flow. The diffusing capacity for carbon monoxide is reduced, and mechanical studies show stiff, noncompliant lungs with decreased elastic recoil. It is not unusual, however, for dyspneic patients with or without chest radiographic findings to have normal lung volumes and diffusing capacities for carbon monoxide. This emphasizes the importance of arterial blood gas measurements during both rest and exercise to detect gas exchange abnormalities. Arterial blood gas determinations in a resting patient typically show hypoxemia, hypocapnia, and respiratory alkalosis. The resting blood gas values may be normal, however, and it is only after the stress of exercise that hypoxemia and a widened alveolar-arterial oxygen difference appear. In a patient who has dyspnea and a normal chest radiograph, these exercise gas-exchange abnormalities also suggest the possibility of pulmonary vascular disease, and additional studies—such as a thin-section chest CT scan—must be done to diagnose IPF.

Gallium Lung Scans

Gallium scans are frequently abnormal in patients with this disorder, but abnormal results are found with other interstitial, malignant, and infectious diseases of the lung, so they have no diagnostic utility. It was originally proposed that the combination of increased gallium uptake by the lungs and an increased number of bronchoalveolar lavage neutrophils indicated an active inflammatory as opposed to a fibrotic histopathologic process. Other investigators have not been able to verify this and have found no correlation between increased gallium uptake and a cellular pathologic pattern. Apparently, however, there is a correlation between both a normal gallium scan and an increased number of bronchoalveolar lavage eosinophils and an underlying fibrotic pathologic picture. We no longer recommend gallium scanning for routinely evaluating patients with interstitial lung disease.

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL), a technique that allows evaluation of the cells of distal airways and alveoli, has been proposed as a procedure that has both diagnostic and prognostic utility in the interstitial lung diseases. Validating the usefulness of this procedure has suffered from a lack of standardized techniques among various investigators and from substantial differences among patients studied. For example, previous BAL fluid studies in patients with IPF did not consider smoking or treatment status. Often, connective tissue

disease-associated interstitial lung disease was not distinguished from IPF, open-lung biopsy material for diagnosis was not available, or the lavage was not done at or around the time of biopsy. Several diseases can be diagnosed by bronchoalveolar lavage (Table 3), but there is no finding from the procedure that characterizes IPF. It was once suggested that the presence of an increased number of neutrophils (normal 0% to 2%) in BAL fluid from these patients indicated an active alveolitis that in turn meant an underlying inflammatory rather than a fibrotic histopathologic disease and, therefore, a greater likelihood of a response to therapy.[13] Subsequent studies have shown that the initial BAL fluid neutrophil counts are not predictive of response to therapy or the underlying pathologic process. In fact, in patients who smoked in addition to having IPF, their BAL fluid neutrophil counts often *increased* after treatment with corticosteroids.[20] This occurred regardless of improvement, worsening, or stabilizing of the clinical course. Subsequent bronchoalveolar lavage in this group of 13 patients indicated that the number of neutrophils found in the fluid from the initial lavage did not predict the outcome.

An increase in the numbers of both neutrophils and eosinophils in BAL fluid correlates with the underlying advanced fibrotic disease and is a poor prognostic sign.[21] BAL fluid lymphocytosis is more characteristic of sarcoidosis, hypersensitivity pneumonitis, silicosis, and lymphocytic interstitial pneumonitis, but about 20% of untreated patients with IPF show an initial BAL fluid lymphocytosis (normal < 15%). This group of patients shows the most constant physiologic improvement after corticosteroid treatment (Figure 4). In addition, correlative histopathologic studies (open lung biopsy) in these patients have consistently shown alveolar wall inflammation—desquamative and early usual interstitial pneumonitis—as opposed to fibrosis. On the other hand, pretreatment BAL fluid neutrophilia without associated eosinophilia does not correlate with either an inflammatory or a fibrotic histopathologic picture and cannot predict response to treatment (Figure 5). A striking number of BAL neutrophils (> 35% of cells) often characterizes the lavage fluid of patients with bronchiolitis obliterans with organizing pneumonia.[7]

TABLE 3.—*Utility of Bronchoalveolar Lavage for Diagnosing Interstitial Lung Disease*

Diagnostic
Alveolar proteinosis—lipoproteinaceous bodies
Malignancy—lymphangitic carcinomatosis, alveolar cell carcinoma, lymphoma
Eosinophilic pneumonia—>30% eosinophils
Suggests the diagnosis
Bronchiolitis obliterans with organizing pneumonia—>35% neutrophils
Diffuse alveolar bleeding—erythrocytes and hemosiderin-laden macrophages
Hypersensitivity pneumonitis or sarcoidosis—>50% lymphocytes
Eosinophilic granuloma—Birbeck granules in pulmonary macrophages by electron microscopy

Lung Biopsy

Because there are no noninvasive diagnostic tests, lung tissue is needed to confirm the diagnosis or, more specifically, to exclude other interstitial lung diseases. It is often relatively easier to implicate a drug-induced or pneumoconiotic interstitial lung disease. The primary lung disorders and those with alveolar findings are often difficult to diagnose by history and physical examination, however.

At the time of bronchoalveolar lavage, it is our practice to do a transbronchial biopsy, particularly if the primary lung and alveolar filling disorders are being considered. If on transbronchial biopsy a specific diagnosis is not made—such as sarcoidosis or alveolar proteinosis—an open biopsy is then done. The diagnosis of IPF should not be made from a transbronchial biopsy, which has no specific diagnostic features and reveals only inflammation and fibrosis. There is a poor correlation between transbronchial and open-lung biopsies.[22] For this reason and because prognostic information can be gained from an open-lung biopsy, we recommend

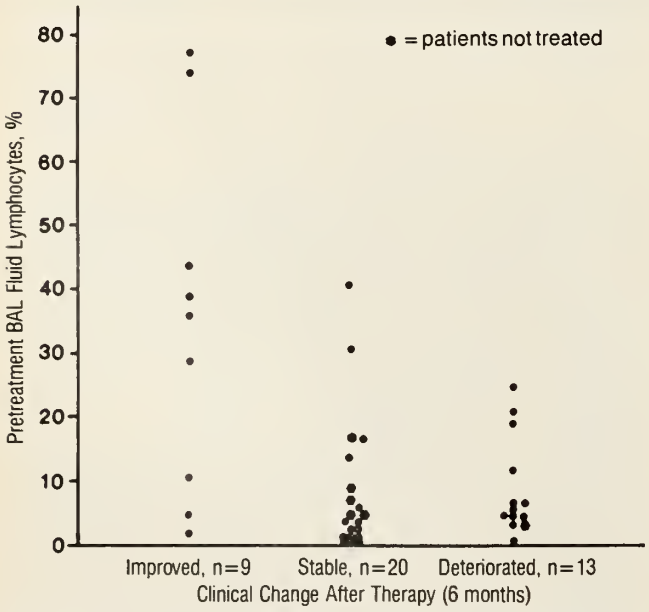

Figure 4.—The graph shows that pretherapy bronchoalveolar lavage (BAL) lymphocytosis (> 15%) predicts therapeutic responsiveness.

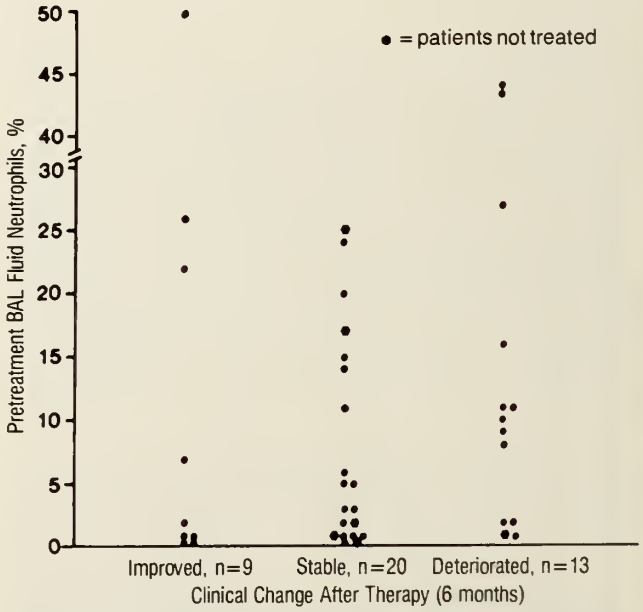

Figure 5.—The graph shows that pretreatment bronchoalveolar lavage (BAL) neutrophilia could not predict response to treatment.

TABLE 4.—*Prognostic Indicators in Idiopathic Pulmonary Fibrosis*

Favorable
Short duration of illness
Serum immune complexes
Bronchoalveolar lavage lymphocytosis
Tissue immune complexes
Active inflammatory process in biopsy specimen
Unfavorable
Clubbing
Radiographic honeycombing
Negative serum and tissue immune complexes
Bronchoalveolar neutrophilia and eosinophilia
Fibrosis in biopsy specimen

TABLE 5.—*Maximum Points Assigned to Clinical-Radiologic-Physiologic Score*

Dyspnea index, 20
Chest roentgenogram, 10
Forced vital capacity, 12
Forced vital capacity in 1 second, 3
Thoracic gas volume, 10
Diffusing capacity, 5
Resting alveolar-arterial oxygen gradient, 10
Exercise gas exchange, 30

open-lung biopsy for all patients with suspected IPF in whom there are no medical contraindications to a surgical procedure.

Treatment

Before treatment is initiated, several prognostic indicators should be considered. Table 4 lists the favorable and unfavorable prognostic indicators in IPF. To initially evaluate and follow the course of a patient with an interstitial lung disease, we have devised a scoring system known as the clinical-radiographic-physiologic (CRP) score.[23] It is derived from an assessment of eight variables: a dyspnea index; a radiographic perfusion score; and six physiologic variables, including the forced vital capacity, the forced vital capacity in one second, the thoracic gas volume, the diffusing capacity for carbon monoxide, and the alveolar-arterial oxygen gradient at rest and with exercise. Maximum points are assigned to each variable (Table 5), and we have found that the composite score correlates better than any of the components with the extent of histologic features on lung biopsy. In general, a CRP score of 0 to 14 points is found in normal persons and scores between 70 and 90 points are found in our sickest patients. For further details about calculating the CRP score, see our article in the *American Review of Respiratory Disease.*[23]

Allowing time for recovery from open-lung biopsy, we generally begin administering prednisone at 1.5 mg per kg of body weight, but not to exceed 100 mg a day, for a maximum of 12 weeks. If improvement or stabilization results, we taper the prednisone dose slowly—1 mg per kg for 6 weeks, 0.5 mg per kg for 12 weeks—continuing treatment for a minimum of a year (0.25 mg per kg). If after the initial 12 weeks there is definite deterioration—an increase in the CRP score—cyclophosphamide, a drug that suppresses T lymphocytes, is added to a reduced-prednisone-dose regimen. Unfortunately, there are no controlled clinical trials of any form of therapeutic maneuver in patients with this disorder. Needless to say, the efficacy of new immunosuppressive therapy such as antilymphocyte globulin or cyclosporine can only be conjectured. Unilateral lung transplantation has had limited success but offers some hope for corticosteroid-unresponsive patients.[24]

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Epitomes

Important Advances in Clinical Medicine

Physical Medicine and Rehabilitation

The Scientific Board of the California Medical Association presents the following inventory of items of progress in physical medicine and rehabilitation. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in physical medicine and rehabilitation that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Physical Medicine and Rehabilitation of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Somatosensory Evoked Potentials in Monitoring Spinal Operations

SPINAL CORD MONITORING is an intraoperative, functional evaluation of spinal cord ascending and descending pathways. While all spinal cord pathways should ideally be evaluated, currently the most practiced application uses somatosensory evoked potentials (SSEPs) to monitor the posterior columns, a major ascending pathway of the spinal cord. Afferents of peripheral nerves enter the spinal cord and ascend in the posterior columns to the medulla, synapsing in the dorsal column nuclei. From there fibers ascend through the medial lemniscus to the thalamus and on to the cerebral cortex.

Somatosensory evoked potentials are recorded repeatedly throughout the operation. The recording principles are similar to those used clinically in that stimulation sites are usually large peripheral nerves—tibial, femoral, peroneal, ulnar, or median nerve, depending on the region of spinal cord or roots at risk. Electrophysiologic recordings are made along the afferent pathway, first of the peripheral nerve to ensure a neural message has been activated and, second, after it has passed the surgical field—that is, epidural space, cervical spine lamina, and the scalp. These signals are of low amplitude, 0.5 to 3 μV, and thus require signal averaging. Epidural electrodes or insulated needle electrodes placed on the vertebral lamina provide a stable response sufficient to reduce the difficulties of a faint signal, electrically noisy environments, and varying responses. Recordings with epidural or insulated needles have been shown to provide a more sensitive monitor of spinal cord function than scalp recordings.

Somatosensory evoked potential monitoring has been used in surgical procedures for scoliosis, spondylolisthesis, fractures, tumors, arteriovenous malformations, dorsal root entry zone lesions, and peripheral nerve repair. Usually SSEP monitoring substitutes for an intraoperative "wake up" test. A loss or reduction of an evoked potential, when reported to the surgeon, usually results in corrective action and signal recovery. Altered SSEPs were recently reported in three cases that were associated with postoperative neurologic deficits despite corrective procedures. Epidural response amplitudes were reduced by more than 30% in 8.5% of limbs studied, suggesting that the technique is sensitive to minor changes in spinal cord conduction.

A future possibility, as indicated by current research, also exists for the monitoring of descending pathways by stimulating the motor fibers of the cortex or spinal cord.

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Scuba Diving for the Handicapped

IN THE PAST, it was considered physicians' responsibility to weed out of eligibility for scuba diving all patients with a neuromuscular disease or other physical disability. Recently, it has become recognized that scuba diving offers mobility-impaired persons a unique opportunity for three-dimensional movement through a gravity-free environment.

Training programs, performance standards, and levels of certification have been developed based not on medical diagnosis but on disabled persons' "buddy dependency" or ability to take care of themselves and their diving companions. This system has already provided access to the submerged two thirds of our planet to persons with paraplegia, quadriplegia, hemiplegia, amputation, cerebral palsy, poliomyelitis, and sensory disabilities such as blindness.

Three levels of certification are recognized based on the degree of "buddy dependency" of a diver and the ability to help a fellow diver in distress:

- *Level A.* Able to provide equal assistance to a fellow diver in case of an emergency. Qualified to dive with another certified diver, including a level A diver.
- *Level B.* Able to care for self in case of an emergency, but cannot provide a fellow diver equal assistance. Qualified to dive with two certified divers who may be at level A.
- *Level C.* Able to safely use scuba gear underwater, but

unable to effectively care for self or fellow diver in case of an emergency. Must dive with two certified divers, one of whom has been trained in diver rescue.

Safety precautions with special significance to disabled divers include the conservative use of dive tables to avoid decompression sickness, caution to avoid abrasions and puncture wounds on insensate extremities, and protection against sunburn or chilling by wearing suitable clothing.

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Electrodiagnosis in Bladder, Bowel, and Sexual Dysfunction

BLADDER, BOWEL, AND SEXUAL DISORDERS are common symptoms of peripheral and autonomic neuropathies, sacral and peripheral nerve injuries, and diseases that affect the brain and spinal cord. New electrophysiologic techniques permit the precise localization and quantification of disturbances in neuromuscular innervation of the bladder, the bowel, and the sex organs. Sacral electrodiagnosis is of clinical importance in the evaluation and subsequent rehabilitation of patients with cervical and lumbar disk disease; pelvic fractures and tumors; arachnoiditis; peripheral neuropathy; spinal cord injury; transverse myelitis; spinal cord tumor; multiple sclerosis; and neurogenic bladder, bowel, and sexual dysfunction.

Electromyography of the perineal sphincters is well established as an important tool in the study of urinary and fecal incontinence and retention. By means of a needle electrode placed directly into the anal or urethral sphincter, signs of acute and chronic degeneration can be found in the striated muscles innervated by the lower sacral segments. Another way to analyze electromyographic activity is to record electrophysiologic patterns by summation and electronic integration. When done with surface or needle electrodes in conjunction with urodynamic studies, detrusor-sphincter dyssynergia can be documented.

The integrity of sacral spinal cord segments S-2, -3, and -4 has classically been evaluated by manually stimulating the glans penis or glans clitoris and observing or palpating contraction of the external anal sphincter. The evaluation of the sacral reflex has recently been refined to the point where sacral cord neural integrity can be recorded and objectively quantified. The bulbocavernosus reflex is evoked electrically by providing an electrical stimulus to the pudendal nerve of the penis or clitoris and recording from the bulbocavernosus muscle, the external anal sphincter, or the external urethral sphincter. The resultant reflex electromyographic deflection, which usually occurs up to 45 ms after stimulation, is an indicator of the integrity of the peripheral somatic sensory and motor pudendal pathways as well as conduction through the sacral spinal cord. Other indicators of sacral neuropathy include a diminished amplitude of the evoked response (less than 50 to 200 μV) and the need for a higher-than-usual stimulus intensity. When the latency of the reflex is more than 7 ms slower on one side than the other, a unilateral lesion is probable, as with a herniated nucleus pulposus. In patients with severe conus medullaris or cauda equina lesions the reflex cannot be elicited at all.

Abnormalities of the autonomic nervous system are often responsible for bladder, bowel, and sexual dysfunction. Applying an electrical stimulus to the proximal portion of the urethra stimulates the afferent autonomic innervation through the hypogastric nerves. The evoked efferent response from the anal sphincter usually occurs within 70 ms after stimulation. This technique significantly enhances the accuracy of the diagnosis of autonomic neuropathies.

Recent applications of digital computer microelectronic averagers have opened the way to spinal and cortical evoked response testing. Somatosensory evoked responses subsequent to pudendal nerve stimulation may be recorded over the L-1 spine at the level of the conus medullaris and over the scalp in the region of the sensory cortex. Spinal evoked responses are of low amplitude—0.1 to 0.5 μV—and difficult to elicit if a patient is obese or if there is even a mild peripheral neuropathy. The cortical evoked response, however, may be consistently recorded electroencephalographically from an electrode placed in the midline of the scalp 2 cm behind the C-2 recording site using the international 10 to 20 electrode placement protocol. The averaging of 256 to 1,024 responses results in a well-formed reproducible response—amplitude 0.5 to 2 μV in male subjects and 0.2 to 1 μV in female subjects. The latencies of onset are similar to those obtained when the posterior tibial nerve at the ankle is stimulated—up to 45 ms.

These electrophysiologic techniques permit a precise assessment of the sensory and motor nerves of the sacral reflex arc and examination of the sacral nerve roots, cauda equina, conus medullaris, and the central nervous systems from sacral cord to sensory cortex. An accurate diagnosis is prerequisite to applying specific rehabilitative methods to treat bladder, bowel, and sexual dysfunctions.

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Robotics for Rehabilitation

COMPUTER-BASED, VOICE-CONTROLLED ROBOTS can enhance the quality of life for a person with high-level quadriplegia, particularly with an injury above the level of C-5 to C-6. Using robots can provide greater control over a person's physical environment, expand avocational and vocational horizons, reduce the expense of attendant care, and improve self-esteem.

Rehabilitation robotics began evolving in the early 1960s with Case Institute of Technology's (Cleveland) computerized orthoses. In the early 1970s, the University of Heidelberg developed an industrial manipulator and minicomputer through which a keyboard controlled by a telephone, typewriter, or a custom mouth-stick could be used for vocational purposes by handicapped persons. In 1981 the Johns Hopkins University's applied physics laboratory designed a more advanced robotic system permitting preprogrammed manip-

ulation sequences for tasks such as retrieving books and serving food. The French Spartacus robotic aid made other contributions to the evolution of the field of robotics.

During the past eight years, the Stanford University and the Veterans Administration Rehabilitation Engineering and Research Center, in collaboration with the Spinal Cord Injury Center (all in Palo Alto, California), have explored through a number of projects the potential use of robots as assisting devices for severely disabled persons. A wide range of users successfully commanded a robot to perform preprogrammed self-care tasks such as providing drinking water, grooming the hair, brushing teeth, and cleaning the face. A third-generation desktop robotic assistant has already been developed and clinically evaluated for persons with high-level quadriplegia. Advances in speech-recognition technology and commercial computer hardware and software have significantly augmented the uses of the system PUMA-260 robot manipulator. Efforts are currently being directed to develop a desktop system that would be useful for a skilled computer scientist in an office setting. The most recent developments in progress include a controlled mobile manipulator consisting of a commercial robotic arm equipped with sensors and mounted on an omnidirectional vehicle, useful to a handicapped person confined to a bed or wheelchair.

Ordinarily no knowledge of computer programming is required to operate the robotic arm; the on-board microprocessor is preprogrammed by a therapist to perform complex tasks in response to one or two commands from the user.

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Prophylaxis and Control of Seizures in Brain-Injured Patients

POSTTRAUMATIC SEIZURES are estimated to occur in approximately 5% of all patients with head injuries and anywhere from 20% to 60% of those with penetrating head injuries. The issue of seizure prophylaxis or treatment following a brain injury often arises in the early days after the injury. Treatment is often instituted with either intravenous phenytoin or phenobarbital in the neurosurgical unit, with conversion to the oral form when the patient is transferred to the rehabilitation service.

Investigators have recently been evaluating the cognitive effects of the use of phenytoin, phenobarbital, or carbamazepine on both persons newly diagnosed with epilepsy and those known to have epilepsy. These studies have important implications for the head-injured population because a disordered cognitive state already exists and further disruption may impede the rehabilitative effort. A comparative study showed little difference in the efficacy of these drugs in controlling tonic-clonic seizures.

In newly referred patients with epilepsy, the use of carbamazepine is associated with a better performance on memory tasks compared with that of phenytoin. Although no significant difference was found on mood ratings between the two drugs, higher blood concentrations of carbamazepine yielded lower ratings for anxiety, depression, and fatigue.

In epileptic patients whose regimen is changed from other anticonvulsants to carbamazepine, tests of memory and concentration show significant improvement. Improved cognitive functioning has also been shown when the number of drugs is reduced without an adverse effect on seizure control.

Although no anticonvulsant study has specifically examined cognitive effects on patients with brain injuries, based on the available data, it seems appropriate to recommend using carbamazepine as the first-line agent in this patient population. Phenytoin is an appropriate alternative if carbamazepine use is not tolerated. Phenobarbital is the least appropriate drug because of its sedative and cognitive effects.

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Advances in Surgical Reconstruction of Upper Extremities in Quadriplegia

THERE IS INCREASING INTEREST in and awareness of the role of surgical reconstruction for paralyzed upper limbs of patients with quadriplegia. A greater number of Veterans Administration and other public and private spinal cord injury centers are offering the possibility of surgical reconstruction to their quadriplegic patients, and an increasing number of patients are undergoing reconstruction in the hope of gaining more independence.

In the past decade novel operative techniques have been developed that extend the possibility of reconstruction to patients with more proximal cervical cord lesions. A useful international classification system has been developed that categorizes patients not on the spinal level of injury but by their remaining functioning upper extremity muscles. As spinal cord injury centers have gained experience with sufficient numbers of patients who have had such operations, ideas about the role and timing of upper extremity reconstruction in the overall rehabilitative process have taken form.

We recently reviewed our ten-year experience at two centers, the spinal cord injury services at the Palo Alto (California) Veterans Administration Medical Center and at Denver's Craig Rehabilitation Institute. During this period more than 400 patients with quadriplegia were examined and more than 170 patients underwent some type of surgical reconstruction for their upper extremity carried out in almost 250 operative procedures. For those patients whose only remaining function was active wrist extension, a one-stage key pinch between thumb and index finger was done (72 limbs). For those patients with a greater number of remaining functional forearm muscles (67 limbs), a two-stage procedure provided both active digital grasp and release and a strong thumb pinch. Active release was accomplished in the first stage and grasp and pinch provided in the second stage. In 40

limbs absent elbow extension was reconstructed by transferring either the deltoid to the triceps muscle or the biceps to the triceps muscle.

Our review has suggested the need to individualize reconstructive planning and to develop a standardized method to evaluate the benefits or deficits that result from upper limb reconstructive procedures. Surgical results are enhanced when specialists in spinal cord and rehabilitation medicine, as well as occupational and physical therapists, are involved in patient selection, the choice of surgical procedures, and aftercare and follow-up. The development and continued nurturing of a harmonious relationship with the specialists who are intimately involved in the total care of quadriplegic patients are vital.

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Sexuality Following Stroke

SEVERAL RECENT STUDIES have reported significant reductions in sexual activity in both younger and older patients following a stroke. A pronounced reduction in libido has been found in both men and women, with a corresponding decrease in coital frequency. The pattern of sexual activity shows a major abrupt change following a stroke. Male patients reported that before a stroke, 95% had erections, 73% had normal ejaculation, and none thought that they had a sexual problem. A year after a stroke, however, only 38% reported normal erections, 22% ejaculated, and 58% thought that they had a sexual problem. Before a stroke, 43% of women reported normal orgasms and 7% felt that they had a sexual problem. At one year after a stroke, only 11% reported having orgasms and 48% felt that they had a sexual problem.

Sexual dysfunction following a stroke may have a number of causes. Impotence may be due to peripheral vascular disease, diabetic neuropathy, or the use of hypotensive medication or tranquilizers. Urologic studies, however, have shown that as much as 90% of all erectile dysfunction is psychogenic, and it is unlikely that these organic factors would be responsible for an abrupt change after a stroke. Further, sexual dysfunction is not due to the direct neurologic features of focal brain lesions, although there have been some case reports of intractable hypersexuality developing following temporal lobe lesions.

For many patients the important factors contributing to sexual dysfunction following stroke are based on behavioral changes. Physical disability and a sense of a loss of attractiveness lead to reduced self-esteem. Patients fear the rejection, or even abandonment, of their partner and are often reluctant to make emotional demands. They usually have some degree of reactive depression. Some patients report a fear that the physical stress of sexual activity may cause another stroke, such as through a rise in the blood pressure. The nature of a couple's relationship may change, with greater focus and attention being given to the details of physical care—transfers, bathing, and personal hygiene. Patients have the concern that these needs be met, and a caring, committed partner gains personal fulfillment through satisfying those physical needs. Involvement in these busy and time-consuming physical activities may be a partial sexual substitute, but they do not satisfy all of the needs of a couple for emotional expression and intimacy.

Physicians can be effective in helping patients and their spouses adjust to all of the consequences of disability from stroke, including sexual dysfunction. Physicians should understand sexuality and life-styles in the aged and learn how to relate empathically to disabled elderly persons. Intimacy may be expressed in different forms, especially in the elderly, but the need for friendship, sharing, and love continues. Physicians should be attentive to these important human needs and be prepared to initiate intervention early in rehabilitation to optimize the total adjustment process following a stroke.

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Ultralight Wheelchairs

WHEELCHAIRS ARE USED FOR MOBILITY, and users may spend hours every day in their chairs. The older wheelchairs are heavy (20 kg [45 lb]), cumbersome to maneuver, and aesthetically unappealing.

The demands by wheelchair athletes for lightweight, higher performance wheelchairs have produced dramatic changes in the manual wheelchair market. In 1979 a California manufacturer introduced the "sports chair." Today's sports chair weighs only 5 to 7 kg (12 to 15 lb) and is custom-made for competition and sports. Ultralight wheelchairs have advantages for all mobility-impaired patients: they are easier to maneuver, require less energy to do so, and are easier to transport.

Most manufacturers of lightweight wheelchairs now produce adjustable, multi-option street chairs that weigh 10 to 14 kg (23 to 30 lb). The wheelchair frames are made from aluminum alloy, stainless steel, or both, with the basic models having rigid or folding frames. A rigid chair provides better performance and durability, but the folding chair becomes compact for transport.

Some typical options for lightweight wheelchairs include adjustable back height; adjustable axle positions, which increases stability; anti-tip devices; removable and adjustable-height armrests; and various frame and upholstery color choices. The built-in adjustability allows a person to set an optimal seat position to further maximize efficient propulsion.

The ultralight wheelchairs have a rapid wheel response and are easier to propel. These characteristics are important

functionally to wheelchair users with impaired trunk, arm, and hand functions.

The cost of lightweight chairs is similar to their heavier counterparts, as the low-option, minimally adjustable chairs start at $700, and the high-option adjustable chairs cost as much as $2,100.

Other suggestions in the purchase of an ultralight wheelchair are professional input in chair and option selection for new wheelchair users and users switching from a traditional to an ultralight wheelchair; a trial use of new or similar equipment; and the careful selection of a competent, dependable wheelchair vendor.

Ultralight wheelchairs offer young, athletic, gravely or minimally disabled, or elderly persons an alternative to a cumbersome, heavy wheelchair.

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Editorials

Votes and Dollars in Health Care

In a presidential election year, the political and social processes that make things happen are very much in the news and attract considerable attention. The driving forces of all this activity are votes and dollars. Politicians seeking to gain or retain public office need both in considerable quantities. They seek both wherever they are to be found, in exchange for promises and commitments—real or implied—that they may or may not wish or be able to honor when they actually gain office. Such is our political system. In the private sector some dollars are diverted for what is called political action—that is, to help candidates for political office get the votes to be elected, with the hope that they will then bear in mind the sources of this support in their actions while in office.

What has all this to do with health care? The impact of both dollars and votes has actually proved to be profound. For example, in the public arena the voting power of the elderly far exceeds that of children and youth, who cannot vote at all. And what has happened? Political support for the care of the elderly is substantially greater than for the care of children and youth, especially the needy. In the private sector, where the dollar reigns supreme, health care is increasingly seen as a profitable or potentially profitable business. The profits are derived from "consumers" who are able to pay, and, conversely, there are no profits, only unwanted costs, when those who cannot pay are served.

This has led to a truly anomalous situation where the elderly, even the rich elderly, receive good health care at government expense, while needed government programs for the children and youth upon whom the future of the nation depends are being curtailed for reasons of economy. The elderly live longer at greater and greater health care expense, while evidence accumulates that the health of youth, particularly disadvantaged youth, is being eroded. And in the private sector, 30 to 40 million Americans are said to be uninsured for health care, many because they cannot afford it or are, for some reason, uninsurable. Something is very wrong.

Votes and dollars are powerful forces in a nation with political and economic systems such as ours. This is the way it is. But these systems, stripped to their essentials, are apt to be without much human compassion, and in themselves offer little incentive for looking or planning beyond the next election or the next foreseeable bottom line. Perhaps another force is needed to influence the votes and dollars that are responsible for health care. If so, this force should be a voice of compassion for human need and a voice for the long-term betterment of the human condition within the political and socioeconomic systems where we must operate. It should be a powerful voice. Physicians and the medical profession are well positioned by interest and training to fill this role. They should be addressing those who vote and those who pay—that is, patients and the public. The campaign for a smoke-free society, which seems to be making good progress, could be something of a model for what can and should be done in the interest of health and well-being in this nation.

MSMW

Physicians and Smoking Cessation

In 1984, Jesse Steinfeld, a former Surgeon General of the United States, wrote in this journal: "Physicians as a group have the lowest incidence of cigarette smoking of any profession or occupation. They also have both the opportunity and obligation to their patients and to society to take a far more active role in eliminating our number one health problem."[1] Earlier this year, Malcolm S. M. Watts commented in the journal: "Cigarette smoking is not only in itself a bad practice, but it can also be good practice for physicians to actively encourage their patients to quit and then find ways to help them do it."[2] In this issue, Prochazka and Boyko outline practical methods that physicians can employ to assist patients to give up smoking.

Although patients are aware of the health risks of smoking, they often do not understand the relative importance of smoking as a cause of preventable death in the United States. For example, in a recent Harris survey of the ten most important things to do to protect one's health, the general public ranked not smoking tenth, behind such items as having a smoke detector in the home and obtaining adequate vitamins and minerals. In the same survey, health professionals ranked not smoking first.[3]

Cigarette smokers experience increased total mortality, compared with nonsmokers, because they are at increased risk to die of five of the six leading causes of death in the US, including coronary artery disease, malignant neoplasms, cerebrovascular disease, chronic obstructive pulmonary disease, pneumonia, and influenza.[4,5] Cigarette smoking contributes to the development of atherosclerosis and the acute ischemic and occlusive vascular events seen with coronary artery disease, sudden unexpected death, cerebrovascular disease, arteriosclerotic peripheral vascular disease, and aortic aneurysm. Cigarette smoke contains carcinogens such as polynuclear aromatic hydrocarbons and nitrosamines, which in susceptible smokers produce cancer of the lung, larynx, mouth, esophagus, bladder, kidney, pancreas, stomach, and uterine cervix. Cigarette smoke contains pulmonary irritants that lead to chronic bronchitis. Smoking also appears to create an imbalance between pulmonary proteases and their inhibitors that results in emphysema.[6]

Cigarette smoking exerts an adverse effect on the outcome of pregnancy; spontaneous abortions, stillbirths, perinatal deaths, and low-birth-weight infants are all more likely if a woman smokes during pregnancy. Smoking also appears to produce adverse long-term effects on the physical growth and intellectual skills of children born to women who smoke while pregnant.

Peptic ulcer disease is more likely to occur, less likely to heal, and more likely to cause death in smokers than in nonsmokers. Cigarette smoking increases perioperative morbidity through its adverse effects on the cardiac, pulmonary, immune, and coagulation systems. It also alters the metabolism of commonly prescribed drugs such as theophylline and β-adrenergic blockers and thus may complicate the medical management of several diseases. Other disorders are observed more frequently in smokers than in nonsmokers, such as osteoporosis, periodontal disease, tuberculosis, infertility,

chronic laryngitis, spontaneous pneumothorax, and Buerger's disease. Involuntary smoke inhalation is a cause of lung cancer in healthy nonsmokers. The children of parents who smoke, compared with children whose parents do not, have an increased frequency of respiratory tract infections and symptoms.

Because nonsmokers live longer and have fewer chronic health problems than smokers, efforts should be directed toward helping children and teenagers maintain their nonsmoking status. Promising educational programs teach students to recognize social influences that encourage smoking and to develop behavioral skills to resist these influences.

Epidemiologic studies document that former cigarette smokers have decreased risks of subsequent morbidity and mortality compared with smokers. Hammond's study of 1 million men and women showed that smoking cessation is beneficial for smokers in all age groups.[7] In this study, mortality rates of former cigarette smokers decreased gradually over time. Ten years after quitting, mortality rates of those who smoked less than 20 cigarettes a day were equivalent to those of nonsmokers. The former smokers who had smoked more than 20 cigarettes a day also showed progressive declines in mortality rates over time, but ten years after quitting, their mortality rates were still higher than those of nonsmokers.

Large prospective studies have established that smoking cessation results in a progressive reduction in mortality rates for the tobacco-related diseases. For coronary artery disease, there may be as much as a 50% reduction in the risk of death within the first year after quitting. For lung cancer and chronic obstructive pulmonary disease, the reduction in risk of death occurs more slowly and may not approach the nonsmoker's risk for 20 or more years after quitting. Smoking cessation is most beneficial when initiated early in life. This is especially true for those disorders such as chronic obstructive pulmonary disease in which smoking causes irreversible damage. Patients with chronic bronchitis and emphysema who quit smoking experience a decline in the prevalence of cough, and their rate of decline in lung function slows to approximate that of age-matched nonsmokers. The adverse effects of smoking on the fetus may be avoided if the mother does not smoke during pregnancy. Patients with peptic ulcer disease heal their ulcers more promptly if they quit smoking.

Smoking cessation is important for all smokers, but it is especially important for those with the highest risks. Young persons who are heavy smokers benefit the most from quitting. Those in high-risk categories because of heredity, occupational or environmental exposures, coexisting diseases or risk factors, and drug exposure should receive special attention.

The steady decline in US smoking prevalence continues. In 1985 an estimated 32.7% of adult men and 28.3% of adult women smoked cigarettes on a regular basis. In the same year in the US, there were about 51 million adult smokers and 41 million adult former smokers. An estimated 95% of these former smokers quit without formal assistance.

Cigarette smoking is an addictive behavior and shares several characteristics with drug dependency involving the use of alcohol, cocaine, and heroin. Some of these characteristics include repetitive and compulsive use, tolerance, and the development of a withdrawal syndrome. A minority of persons with addictive behaviors such as cigarette smoking achieve and maintain abstinence with their first attempt; knowledge of this point may help health professionals to have more realistic treatment goals and may help smokers to understand the course leading to cessation.

Physician intervention is effective in assisting patients to stop smoking.[8] Prochazka and Boyko correctly point out, however, that "the great potential for physicians to intervene in the smoking cessation process has not been realized." The practical guidelines proposed by these authors include identifying the smoking habit, providing brief counseling and self-help programs, and following up to help prevent relapse. They also outline a more intensive intervention program that emphasizes a "behavioral smoking cessation plan," the use of nicotine gum in selected patients, and maintaining abstinence. Prochazka and Boyko reviewed the few studies that used nicotine gum combined with brief advice; they concluded that the gum should not be used in this situation. Additional studies are needed before firm judgments can be made on whether nicotine gum should be used in the traditional office setting.

Physicians have the opportunity to assist their smoking patients by functioning as clinical counselors. The first step is to accept cigarette smoking as a chronic medical problem requiring treatment and to note this on the problem list. Thereafter, the patient should receive a personalized message concerning the risks of smoking and a self-help pamphlet on quitting. The treatment program should be individualized because no single method has been found to be superior to any other; the "cold turkey" approach appears to be more effective than the "tapering" approach, however. An understanding of tobacco dependency and the tobacco withdrawal syndrome aids the clinical counselor to anticipate obstacles and to help the patient achieve and maintain abstinence. The patient should be encouraged to set a quit date and should be scheduled for a follow-up appointment with the physician. If a more comprehensive treatment program is required, referral to a smoking cessation specialist should be arranged.

Most physicians are nonsmoking role models. Many physicians are working in societal roles to help achieve a smoke-free environment. Beyond these efforts there is a great need for more patients to receive personalized smoking cessation assistance from their physicians. The National Cancer Institute is supporting five major smoking cessation trials involving physicians and dentists.[9] Residency training programs for the development of smoking intervention skills are also being implemented.[10] Widespread clinician involvement in smoking cessation programs will also depend on third-party reimbursement for clinical counseling. As these training and reimbursement issues are resolved, "the great potential for physicians to intervene in the smoking cessation process" may be realized.

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Euthanasia—The Continuing Debate

THE DEBATE OVER ACTIVE EUTHANASIA again has captured public and professional attention because of the de facto legalization of active voluntary euthanasia in the Netherlands,[1] a drive in the spring of 1988 to place a proposition legalizing euthanasia on the California ballot, and the publication of the case vignette, "It's Over, Debbie," in *The Journal of the American Medical Association (JAMA).*[2] The lucid and eloquent article by Professor Albert Jonsen elsewhere in this issue is an important contribution to this discussion. Several points in his article deserve elaboration or emphasis.

The Importance of Clear Terminology

The debate over euthanasia is sometimes marred by ambiguous terminology and rhetoric. Several practices in the care of dying patients should be distinguished. "Active euthanasia" is sometimes called direct killing. Euthanasia is called voluntary when a patient requests it.

Active euthanasia is generally distinguished from withholding or withdrawing treatment (also termed "allowing to die" or "passive euthanasia"). As Jonsen explains, in some cases the moral line between withholding treatment and active euthanasia may be difficult to draw. Such difficult cases, however, are exceptions to a general rule of thumb that separates these two practices. Concern that active euthanasia is unethical should not lead physicians to continue futile treatments or to reject requests by competent, informed patients to withhold or withdraw treatment. Prolonging life is not always the appropriate goal of medical care. A medical, ethical, and legal consensus has developed that physicians should respect refusals of treatment by informed, competent patients, even if their lives will be shortened. Furthermore, prior refusals of treatment by incompetent patients should also be respected.[3,4]

Assistance with suicide may be requested by some patients. For example, a man with end-stage acquired immunodeficiency syndrome may believe that living with pain, fatigue, progressive disfigurement, and uncontrolled diarrhea is degrading and may wish to have control over his death. He might ask his physician how to end his life or request medications to do so. Suicide differs from the other actions discussed here because the patient's own actions lead to death. In such patients, a wish to commit suicide might be considered rational because their conditions are irreversible. In contrast, the vast majority of patients who seriously consider suicide have clinical depression that is likely to respond to changes in the psychosocial situation, counseling, or taking antidepressants. Because persons incapacitated by depression cannot make autonomous or informed decisions, physicians have a duty to intervene so that they do not harm themselves.

Many physicians oppose assisted rational suicide for the same reasons that Jonsen opposes active euthanasia. Furthermore, the law in most states prohibits assisted suicide. Some physicians and commentators, however, condone assisted rational suicide, arguing that death results from the patient's actions, rather than from those of the physician.[5]

Another practice is giving doses of analgesics that might hasten death. This practice is discussed next in more detail.

The Importance of Supportive Care

For most patients, a request for active euthanasia may represent a cry for help, a fear of abandonment, a demand for more control over their care, or a way to call attention to physical or emotional pain. In Holland, 85% of patients with terminal illness who request active euthanasia change their minds after they receive better relief of their symptoms (P. Admiraal, MD, written communication, October 30, 1987). Thus, ethical debates over active euthanasia can often be resolved clinically by improving supportive care for a patient. In the United States, 20% of patients with metastatic cancer experience unrelieved severe pain during their last weeks of life.[6] Other dying patients may suffer from severe dyspnea, for instance, from end-stage chronic obstructive lung disease or from *Pneumocystis carinii* pneumonia that has not responded to the use of antibiotics. Even when physicians cannot cure the underlying disease or its complications, they can relieve both physical and emotional suffering and, indeed, have an ethical duty to do so.

In such cases, the physician should give analgesics and sedatives to control symptoms. We have learned a great deal about how to use analgesics effectively[7,8]: The dosage should be gradually increased until symptoms are relieved. Regular doses are more effective than "as needed" dosing. Behavioral, neurosurgical, and anesthetic approaches to pain control need to be considered, and attention to emotional and spiritual pain is essential. Giving patients control over the timing of medications can also be effective. No predetermined dosage limit should be set, since such patients may require much larger doses than are needed for acute pain. Side effects should be anticipated and treated. A patient's response should be carefully monitored.

We also have learned some common errors in managing pain. Doses of analgesics that are prescribed by physicians or administered by nurses may be too low to achieve the desired relief of symptoms. Often doses are restricted because of concerns about addiction, but such concerns should not be paramount in patients who will die in a short time.

In most cases, pain can be relieved without depressing consciousness or respiration. When, however, relief requires doses that cause these side effects, ethical and emotional dilemmas occur. The traditional doctrine of "double effect" justifies using such high doses: The physician intends to control pain, this laudable goal cannot be achieved without also causing the undesirable effects, and it is better to relieve symptoms in patients with terminal illness than to allow them to suffer. It is essential, of course, that lower doses be shown to be ineffective and that the lowest dose that relieves symptoms be used.

The Danger of Abuse

Opponents of active euthanasia commonly raise practical objections. They fear that the potential for abuse is great and that voluntary euthanasia can all too easily lead to involuntary

euthanasia. As Jonsen points out, the *JAMA* article aroused much indignation because the killing it described was not voluntary. Debates over euthanasia are sometimes polarized by assertions that advocates of the practice are opening the door to genocide, as occurred in Nazi Germany. While it is important to acknowledge the historical precedent, slogans or name-calling may be counterproductive.

The question of whether a policy of active euthanasia will lead to abuses can potentially be decided by empirical facts. Some proponents of active euthanasia cite the Dutch experience with de facto legalization as reassurance that abuses will not occur. The absence of reports of abuse, however, does not guarantee that abuses do not occur. We must appreciate the possibility of type II errors. Information about euthanasia in Holland is based on anecdotal or journalistic accounts. No review has been published that examines the quality of decision making and supportive care in a series of consecutive cases of active euthanasia. Given the lack of data on possible abuse, we might ask where the burden of proof should lie. It is prudent to assume that abuses may occur unless we have strong evidence that they do not, rather than the reverse.

Attention to the possible abuses with active euthanasia should not lead physicians to overlook errors in decisions to withhold or withdraw treatment. We may be mistaken when making a diagnosis, assessing prognosis, or ascertaining patients' preferences. Competent patients or families of incompetent patients do not participate in about 20% of "do not resuscitate" decisions, despite guidelines that they should do so.[9] Physicians commonly assume they know their patients' preferences without asking explicitly; studies have shown that this is not the case, however.[10]

The Impact on Other Patients

Jonsen's argument that active euthanasia is incompatible with the special role of physicians has also been forcefully expressed by others.[11] It is worth noting that public opinion polls that report substantial support for active euthanasia may not refute this argument. Typically in such polls, respondents are asked whether they approve of physicians actively killing terminally ill patients who want their lives ended. Respondents are not asked how they would feel being a patient of a physician or a hospital that practiced active euthanasia if they were not terminally ill or did not want active euthanasia. Would patients still trust that their physicians were acting to benefit them? Or would there be nagging doubts that physicians did not always provide beneficial treatments that patients wanted, perhaps because care was too costly or because patients were considered unworthy? Even the suspicion or appearance of abuse may damage the role of physicians.

Exceptions to a General Prohibition on Euthanasia

While physicians may focus on individual cases that present difficult decisions, philosophers remind us that we need to base our actions on universal rules or principles. Furthermore, we must consider the long-term and indirect consequences of our actions in particular cases. For example, Jonsen reminds us that the long-term effects of active euthanasia on the physician-patient relationship must not be overlooked. On the other hand, it may be helpful to distinguish a general prohibition of active euthanasia from allowing it in exceptional cases.[12] In unusual cases, it may seem more compassionate to carry out a patient's request for active euthanasia than to have the patient continue to live an existence that he or she feels is degrading, in which debilitating symptoms cannnot be adequately relieved. Some physicians have suggested that euthanasia be condoned in exceptional cases: a conscientious physician, after weighing the ethical, medical, and legal prohibitions against active euthanasia, might decide that a particular case is an exception and accept the consequences of performing an illegal act. Surveys of physicians suggest that such exceptional cases may indeed occur.[13]

The question of active euthanasia will continue to be discussed by our patients and the public. Physicians need to think about these issues, discuss them with patients, and contribute to the ongoing public debate.

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Case Reports

Pericarditis With Effusion and Tamponade Complicating Left Subdiaphragmatic Abscesses

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ALTHOUGH NONSUPPURATIVE PLEURAL EFFUSIONS have been associated with subdiaphragmatic abscesses, analogous pericardial effusions as sequelae of subdiaphragmatic abscesses are not described in standard references.[1-4] Manual searches of *Quarterly Cumulative Index* from 1916 through 1926, of *Quarterly Cumulative Index Medicus* from 1927 through 1956, of *Current List of Medical Literature* from 1957 through 1959, and of *Cumulated Index Medicus* from 1960 through 1965 and a computerized search of *Cumulated Index Medicus* from 1966 through 1986 uncovered no references of direct relevance. We report four cases of sympathetic pericardial effusion associated with left subdiaphragmatic abscesses. In two cases, cardiac tamponade with cardiopulmonary arrest occurred, with a fatal outcome in one.

Patients and Methods

We reviewed the charts of all patients discharged from three Charlotte, North Carolina, hospitals—Charlotte Memorial Hospital, Presbyterian Hospital, and Mercy Hospital—from July 1984 through June 1986 with a diagnosis of peritonitis or intra-abdominal abscess (ICD-9-CM code 567.2).[5] Cases were evaluated for the presence of pericarditis, pericardial effusion, or tamponade. Evidence of pericardial disease by auscultation, echocardiogram, pericardiocentesis, surgical procedure, or autopsy was required for inclusion.

Statistics

The frequency of pericardial disease with right and left subdiaphragmatic abscesses was compared using the Fisher's exact test.*

Results

Of 182 cases of intra-abdominal infections, 4 of 20 cases of subdiaphragmatic abscess had associated pericardial disease (Figure 1). Of eight cases of left subdiaphragmatic abscess, five had an associated left pleural effusion, four of which also had recognized pericardial involvement. Of 12 cases of right subdiaphragmatic abscess, 3 had right pleural effusions or empyema, 1 had right and left pleural effusions, and none had recognized pericardial involvement. Eight cases of intra-abdominal infection not localized to the subdiaphragmatic spaces had pleural effusions, but no cases of pericardial disease complicating intra-abdominal infections other than subdiaphragmatic abscesses were identified.

*The statistical analysis was done by Rachel Ballard-Barbash, MD, of the Nalle Clinic.

(Horton JM, Tucker WS Jr: Pericarditis with effusion and tamponade complicating left subdiaphragmatic abscesses. West J Med 1988 Aug; 149:213-215)

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This study was presented as a poster at the American Federation for Clinical Research Southern Section meeting January 1987.

Dr Tucker is a Teaching and Research Scholar of The American College of Physicians.

Reprints are not available.

Reports of Cases

CASE 1. The patient, an 82-year-old-woman, presented with left chest pains. She had had many abdominal operations and had congestive cardiomyopathy, sick sinus syndrome treated with a permanent pacemaker, and recurrent urinary tract infections. Three months previously, left upper quadrant pains and low-grade fever had led to an admission to hospital; an *Enterobacter* urinary tract infection was treated with the administration of doxycycline. One month before this admission, nitrofurantoin was given after urethral dilatation.

Three days of epigastric and left lower chest pains, nausea, vomiting, and diarrhea prompted a readmission to hospital. There was pronounced epigastric and mild left costovertebral angle tenderness. A chest x-ray film showed cardiomegaly. A barium enema film showed diverticula. Abdominal ultrasonography and intravenous pyelography were normal. Giardiasis diagnosed by endoscopic duodenal aspiration was treated with the administration of metronidazole hydrochloride. Fevers to 39.5°C (103°F) began.

Pericardial and left pleural rubs were noted on hospital day 3. Thoracentesis of left pleural fluid showed an exudate with a pH of 7.1, an amylase level of 40 units per dl (400 units per liter; normal for serum, 15 to 200 [150 to 2,000]), a protein level of 4.1 grams per dl (41 grams per liter), and a leukocyte count of 1,000 per μl (1.0×10^9 per liter). Echocardiography showed a small pericardial effusion. A computed tomographic (CT) scan of the abdomen suggested a splenic infarction. *Escherichia coli* was cultured from a percutaneous splenic aspirate. Therapy with cefoxitin was begun; a splenectomy confirmed the diagnosis of splenic infarction with abscess, which was densely adherent to the left subdiaphragmatic surface. Her recovery was uncomplicated.

CASE 2. The patient, a 16-year-old woman, had had abdominal cramps for three days. She had right lower quadrant guarding and a temperature of 38.3°C (101°F). A regimen of cefoxitin was begun. A ruptured appendix with a local abscess was found at laparotomy. Drains were placed, and gentamicin sulfate was added to her regimen. She had persistent fevers, so cefotaxime sodium and clindamycin were given. On postoperative day 6, a pericardial rub and a left pleural effusion developed; a moderate pericardial effusion was shown echocardiographically. Later, mezlocillin and metronidazole were given. Turbid pleural fluid removed by thoracentesis clotted, and cultures were sterile. On days 8 and 14, CT scans showed a left subdiaphragmatic abscess and increasing pericardial and bilateral pleural effusions. Cultures of abscess fluid obtained by percutaneous drainage were sterile.

On day 15, she became dyspneic, tachypneic, and agitated with hypotension and a paradoxic pulse of 20 mm of mer-

cury. She had periorbital edema, distended jugular veins, and distant heart sounds. An electrocardiogram showed low voltage. The central venous pressure was too high to measure with a manometer. A cardiac arrest from tamponade was treated successfully, and pericardiocentesis of 250 ml of serosanguineous fluid improved her hemodynamics. Fluid analysis showed a protein level of 3.9 grams per dl (39 grams per liter), a glucose level of 100 mg per dl (5.4 mmol per liter), and an erythrocyte count of 1.74×10^6 per μl (1.74×10^{12} per liter). The fluid leukocyte count was 2,600 per μl (2.6×10^9 per liter) with a differential count of 36 segmented neutrophils, 39 bands, 4 lymphocytes, 5 eosinophils, 4 metamyelocytes, 1 myelocyte, 1 tissue cell, and 8 nucleated erythrocytes. Cultures for bacteria, mycobacteria, and fungi were sterile. After the arrest, she had a transient coagulopathy. An antinuclear antibody titer of 1:1,280 in a speckled pattern was attributed to the severe infection. On day 24, a pericardiectomy revealed 300 ml of bloody pericardial fluid and fibrinous pericarditis, and a laparotomy showed a resolving left subdiaphragmatic abscess. *Candida* sepsis was treated with the administration of amphotericin B. Further recovery was uneventful. During 18 months of follow-up, no evidence of systemic lupus erythematosus has developed.

Case 3. A 27-year-old woman had left lower quadrant pain for one day. She had a distant history of splenectomy after a motor vehicle accident, and she had been treated for pneumonia one month previously. On hospital admission, she had a blood pressure of 100/60 mm of mercury, a pulse of 140 beats per minute, and a temperature of 40°C (104°F). The abdomen was rigid and had diffuse rebound tenderness. Therapy with cefazolin, clindamycin, and gentamicin was begun; later, cefoxitin was given. At laparotomy a pelvic abscess was noted, and blood and peritoneal cultures grew *Streptococcus pneumoniae.*

On hospital day 3, a chest x-ray film showed an enlarged cardiac silhouette and left pleural effusion. An electrocardiogram was normal on day 4. Persistent fevers by day 7 led to ultrasonographic and CT scanning, showing a left subphrenic abscess and minimal pericardial fluid. A percutaneous aspirate of 75 ml of pus from the abscess showed many neutrophils but no organisms on Gram's stain; cultures were sterile. An echocardiogram showed a pericardial effusion. She recovered smoothly. On day 20, a repeat echocardiogram showed a small pericardial effusion. After late resolution of her fever, she recovered smoothly.

Case 4. The patient, a 34-year-old man with hypertension and recurrent familial pancreatitis, had abdominal pain for four hours. He was afebrile and had a blood pressure of 160/120 mm of mercury. Generalized abdominal distension without rebound tenderness was present, and bowel sounds were absent. A serum amylase level was 104 units per liter (normal 25 to 115).

On hospital day 1, a right internal jugular venous catheter was inserted, and a serum amylase level was 418 units per liter. On day 2, the administration of parenteral nutrition was begun. On day 4, a left subclavian venous catheter was placed and a fever to 39°C (102.2°F) developed. Cefazolin therapy was begun but was changed to imipenem-cilastatin sodium. On day 5, the left subclavian catheter was removed because of insertion site cellulitis and a right internal jugular venous catheter was inserted. Blood cultures grew *Staphylococcus aureus.* The imipenem-cilastatin therapy was stopped and cefazolin therapy resumed.

On day 9, he became dyspneic and hypotensive. An electrocardiogram showed a sinus tachycardia. Pulmonary embolism was suspected, and heparin was given briefly pending

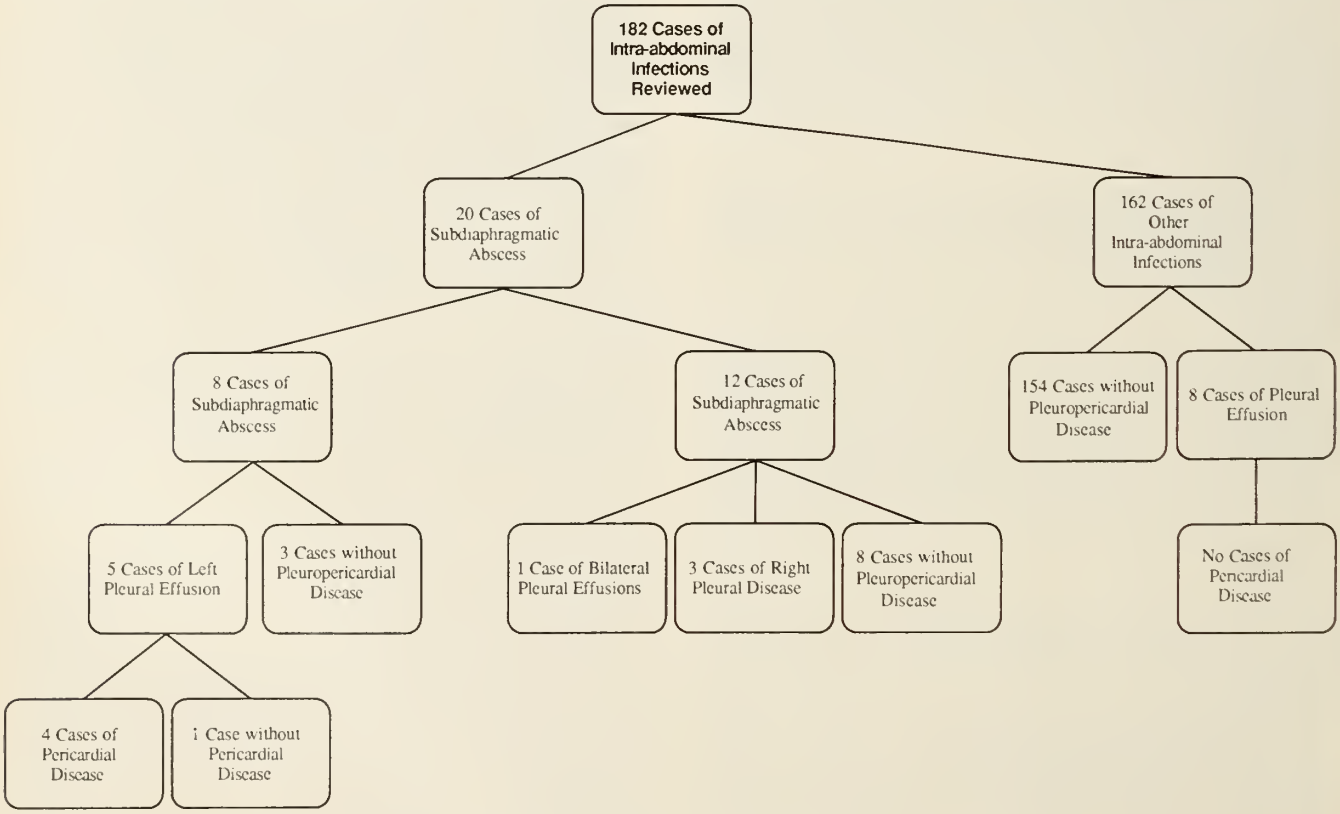

Figure 1.—The diagram shows 182 cases of intra-abdominal infections reviewed.

the outcome of a radionuclide ventilation-perfusion scan, which was normal. Cardiac tamponade was diagnosed echocardiographically. A cardiac arrest occurred as an emergency pericardial window was created, releasing tense fluid. The clear amber pericardial fluid had a protein level of 0.7 grams per dl (7 grams per liter), a specific gravity of 1.016, a glucose level of 2,046 mg per dl (109 mmol per liter) with a blood glucose level of >400 mg per dl (>21 mmol per liter), and an amylase level of 0 units per liter. No fluid cultures or cell counts were done. No cardiac perforation was found. The antibiotic regimen was changed to nafcillin sodium and later to vancomycin hydrochloride with tobramycin. The patient died on day 20 of ischemic encephalopathy. An autopsy revealed pancreatic fibrosis and atrophy, pulmonary emboli, fibrinous pericarditis without cardiac perforation, a left pleural effusion, and a 1-cm perforated gastric ulcer with a loculated left subdiaphragmatic abscess.

Discussion

The classic review of subdiaphragmatic abscesses by Ochsner and DeBakey from 1938 acknowledged thoracic complications of subdiaphragmatic abscesses, including empyema, bronchial fistula, and pericarditis.[6] In that preantibiotic era, however, most, if not all, of these complications probably were suppurative, occurring from direct penetration or perforation of infection through the diaphragm or from bacteremic colonization of effusions.[7] To the best of our knowledge, in the past 50 years, with one possible exception,[8] the pericarditides reported with subdiaphragmatic abscesses have been suppurative in nature and have occurred with infections penetrating through the diaphragm. Our four cases support an association between nonsuppurative, sympathetic pericardial effusions and left subdiaphragmatic abscesses. In contrast to none of 12 cases of right subdiaphragmatic abscess we reviewed, 4 of 8 cases of left subdiaphragmatic abscesses had pericardial findings. The association of pericardial disease with left subdiaphragmatic abscesses was statistically significant ($P = .014$), although we cannot be certain that patients with right and left subdiaphragmatic abscesses were equally likely to be evaluated for pericardial disease.

In our series, pericarditis and pericardial effusions were recognized four to nine days after the onset of symptoms of abdominal infection. Symptoms included chest pain and dyspnea. Cardiac tamponade occurred in two cases and was ultimately fatal in one. In only one patient (case 3) was the pericardial process apparently silent and discovered fortuitously by sensitive technologic means, such as CT scanning. Even with early detection of pericardial fluid in case 2, however, the potential for cardiac tamponade was underappreciated and that catastrophe was not averted. Two patients (cases 1 and 3) had pericardial fluid shown by echocardiography. The two other patients (cases 2 and 4) had pericarditis with effusion confirmed by pericardiocentesis, pericardiectomy, or autopsy.

In none of the four cases was there evidence of purulent pericarditis. Pericardial fluid cultures were negative in case 2, although antibiotics had been given. The patient had an elevated antinuclear antibody titer, but 18 months later she had no evidence of autoimmune disease that might have caused the pericarditis. The patient in case 4 had an elevated glucose level in the pericardial fluid, possibly suggesting central venous catheter perforation, but no evidence of cardiac perforation was found at operation or at autopsy. Although patients 2 and 4 had bleeding diatheses during their illnesses, pericardial fluid found in each case was not consistent with hemopericardium. None of the four patients showed pancreatic pleuropericardial effusions.

The pathophysiologic mechanism for sympathetic pericarditis with effusion in the setting of subdiaphragmatic abscess is unknown. Pleural effusions are recognized to occur from subdiaphragmatic infections on either the right or the left.[6] These pleural exudates may be caused by changes in capillary permeability or lymph flow in the diaphragm induced by local effects of inflammatory products.[2,6,9,10] We hypothesize a similar mechanism for the pericardial findings in our series. The proximity of subdiaphragmatic inflammatory processes to the pericardium overlying the left diaphragm may be a key factor in determining whether pericardial complications develop. With relatively little liver mass adherent to the left subdiaphragmatic surface, abscesses there have exposure to a large area over which the pericardium lies.[11]

Each patient presented with infection, not with pericardial disease. With treatment with potent, broad-spectrum antibiotics and with surgical interventions, mortality from uncontrolled infection was nil. The indirect pericardial complications of the left subdiaphragmatic abscesses in our series were serious, however, posing life-threatening risks and requiring costly and invasive procedures for management.

Conclusion

In patients with subdiaphragmatic abscesses, early recognition of sympathetic pericarditis with effusion may be lifesaving. Especially if a left pleural effusion is present, evidence of pericarditis should be aggressively sought by bedside examination, echocardiography, abdominal ultrasonography, or CT scanning. Conversely, subdiaphragmatic abscesses should be sought when pleuropericardial exudates are otherwise unexplained.

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Recurrent Spontaneous Infected Pleural Effusion in a Patient With Alcoholic Cirrhosis, Hepatic Hydrothorax, and Ascites

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HYDROTHORAX DUE TO CIRRHOSIS is usually right-sided and has been attributed to defects in the diaphragm allowing the passage of ascitic fluid into the pleural cavity.[1] Other suggested mechanisms include hypoalbuminemia, hypertension in the azygous or hemiazygous systems, and the presence of lymphatic channels in the diaphragm. In this report we document a case of right-sided pleural effusion related to cirrhosis. The effusion was initially associated with clinically detectable gross ascites. The subsequent detection of minimal ascites over an 18-month period required sonography. The transfer of the fluid from the abdominal cavity to the pleural sac has been referred to as hepatic hydrothorax.[2] We describe a simple nuclear medicine imaging technique to document the transdiaphragmatic migration of ascitic fluid. The patient's course and results of investigations are suggestive of recurrent episodes of spontaneous bacterial infection of the ascitic fluid followed by transdiaphragmatic migration of this fluid into the pleural cavity.

Report of a Case

The patient, a 38-year-old man with a history of alcoholism, was admitted to 2 different Veterans Administration facilities on 13 occasions over an 18-month period. These admissions were precipitated by the recurrence of abdominal pain, rigors, dyspnea, and fever. Physical examinations invariably revealed fever and mild icterus in the presence of hepatosplenomegaly and cutaneous stigmata of cirrhosis. A large right-sided pleural effusion and, on the initial occasion, clinical signs of ascites and peripheral edema were detected. Blood laboratory values showed a normal hemoglobin and hematocrit with a leukocyte count ranging from 9,000 to 12,000 per μl, predominantly neutrophils. His serum aminotransferase level was raised slightly, as was the bilirubin level, and the serum albumin value was 2.0 grams per dl. A serologic test for viral B markers was negative. The pleural fluid contained leukocytes ranging in number from 3,080 to 7,500 per μl that were predominantly neutrophils. The protein content was 0.75 grams per dl and cytologic findings were normal. Repeated pleural fluid aerobic and anaerobic cultures were negative for routine organisms and tuberculosis. A pleural biopsy showed a mild, nonspecific chronic inflammation. The findings of a computed tomographic scan, liver and spleen imaging, and an ultrasonogram were characteristic of cirrhosis with portal hypertension.

On the initial admission, an ascitic paracentesis was successful, eliciting the following results: appearance cloudy; leukocyte count, 10,666 per μl; differential, 81% polymorphonuclear leukocytes, 10% monocytes, and few mesothelial cells. Culture of paracentesis fluid showed no growth. (Simultaneous pleural fluid aspiration was not attempted.) On one of his many admissions for fever and abdominal pain, *Escherichia coli* and, on another occasion, *Staphylococcus aureus* were grown from the blood cultures.

Broad-spectrum antibiotic coverage was usually started, and this invariably resulted in a rapid resolution of his fever and abdominal pain. On one occasion, a repeat pleural fluid leukocyte count decreased from 4,500 to 400 per μl and on another occasion from 3,080 to 205 per μl shortly after antibiotics were administered. The pleural fluid pH was 7.30 and the arterial pH was 7.48. The chest radiograph on every occasion showed a right-sided pleural effusion without any underlying parenchymatous disease, and all attempts at aspirating pleural fluid were successful. Ascitic fluid was successfully aspirated only during the patient's first admission and during ultrasound guidance on the occasion of a peritoneopleural imaging study.

To show that the right pleural effusion reflected the nature of the ascitic fluid, a peritoneopleural imaging study was done. The diuretic therapy was temporarily discontinued to facilitate an accumulation of ascitic fluid. Under ultrasound guidance, a small amount of ascitic fluid was located and aspirated. Then 5 mCi of technetium ^{99m}Tc sulfur colloid was added to 10 ml of ascitic fluid, and the fluid was reinjected into the peritoneal cavity in the left lower quadrant. The patient was instructed to move freely for ten minutes. Then images of the upper abdomen and chest were taken at 15 and 30 minutes and at 1 hour, 3 hours, and 5½ hours with a low-energy, all-purpose collimator and large-field-of-view γ camera (Siemens Medical Systems, Inc, Des Plaines, Illinois). At this stage a specimen of right pleural fluid and blood was aspirated and its radioactivity counted in a well counter. The images clearly showed the ^{99m}Tc sulfur colloid activity in the right pleural space (Figure 1). The pleural fluid aspirated at 5½ hours after the initial radiopharmaceutic injection into the ascitic fluid showed a 9½ times higher activity compared with the blood. Both the images and the pleural fluid radioactivity confirmed the presence of a peritoneopleural connection.

Discussion

Approximately 5% of patients with cirrhosis and ascites have an associated, usually right-sided, pleural effusion.[3] Pleural effusions caused by cirrhosis but not associated with clinical ascites have been reported previously.[3-8] The plausible pathogenesis is that the cyclic negative intrathoracic pressures associated with respiration enhance the transdiaphragmatic migration of ascitic fluid into the pleural cavity. Lieberman and Peters were able to show the presence of defects in the diaphragm in four patients with cirrhotic hydrothorax.[1] Leak and Rahil have been able to demonstrate, by using transmission and scanning electron microscopy, the migration of peritoneal cells onto the surface of the diaphragm through pores in the diaphragm.[9] When the circumstances are appropriate and the index of suspicion of a he-

(Baylor PA, Bobba VVR, Ginn PD, et al: Recurrent spontaneous infected pleural effusion in a patient with alcoholic cirrhosis, hepatic hydrothorax, and ascites. West J Med 1988 Aug; 149:216-217)

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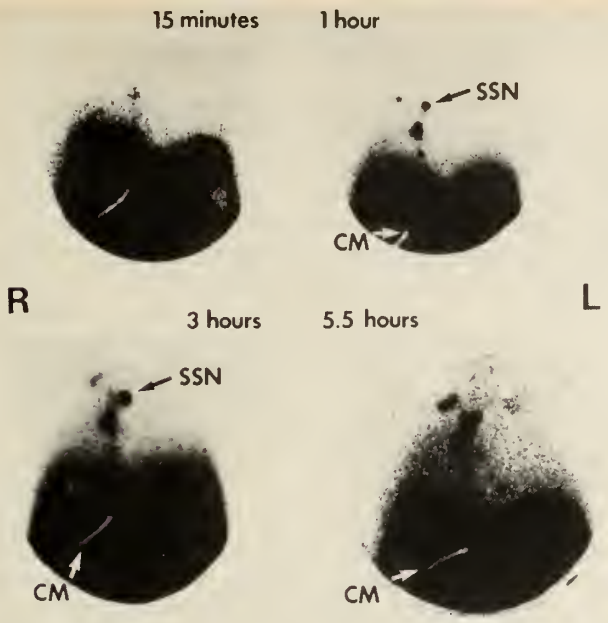

Figure 1.—Anterior images of the upper abdomen and chest were taken as noted after administering 5 mCi of technetium Tc 99m sulfur colloid into the peritoneal cavity in the left lower quadrant by paracentesis. Note the ^{99m}Tc sulfur colloid activity in the right pleural cavity at 1 hour, which becomes more intense at 5½ hours, confirming a peritoneopleural connection. CM = costal marker, L = left, R = right, SSN = suprasternal notch

patic hydrothorax with ascites is high, but there is no clinical evidence of ascites, then sonography is indicated to confirm the presence or absence of ascites. If ascites is present, an intraperitoneal injection of a radiopharmaceutic agent followed by serial imaging of the chest and upper abdomen is the recommended technique to document the peritoneal origin of the pleural effusion.

Diagnosing spontaneous bacterial peritonitis requires a positive culture of the ascitic fluid; Runyon and Hoefs, however, suggested that culture-negative spontaneous bacterial infection can also occur, and they have termed the process culture-negative neutrocytic ascites.[10] Thus, the fever, rigors, and abdominal pain in this patient suggest spontaneous bacterial infection of the ascitic fluid with some of this fluid migrating into the pleural cavity. This appears to have occurred because of a defect in the diaphragm permitting a ready communication between the ascites and pleural fluid. Of further interest was the chronic, recurring nature of the patient's course and the rapid resolution once antibiotic treatment was started.

An underwater drain of the pleural fluid associated with ascites is contraindicated in the light of adverse experiences documenting a rapid depletion of the intravascular volume with shock.[11] Perhaps, as suggested by Runyon and coworkers,[12] with more selective and sophisticated culture techniques, the number of cases of culture-negative neutrocytic ascites and pleuritis can be reduced.

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Diabetic Ketoacidosis With Alkalemia—A Review

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ACCUMULATION OF ACETOACETIC and β-hydroxybutyric acids results in ketoacidosis, a common complication in patients with diabetes mellitus. A less often recognized metabolic alteration is "diabetic ketoalkalosis," a term coined by Bleicher.[1] This syndrome is a mixed acid-base disturbance in which diabetic ketoacidosis coexists with a metabolic alkalosis. In such situations, the blood pH is determined by the predominant disorder. Patients with diabetic ketoacidosis can, therefore, have a high pH or alkalemia if they have a disorder that causes a superimposed metabolic alkalosis. Since the initial report,[1] 18 more cases have been reported in the literature.[2-15] Vomiting,[1-5,7,9,12,13] diuretic use,[8,9,11,13,14] and alkali ingestion[1,4,15] have been implicated as causes of this disorder. We describe the third case of hypercortisolism as the underlying cause of diabetic ketoacidosis with alkalemia.

Report of a Case

The patient, a 50-year-old woman, was admitted to hospital because of weakness, polyuria, and polydipsia for one week. She had had hypertension for five years, treated with propranolol hydrochloride and hydrochlorothiazide. She said she did not have vomiting nor did she ingest alkaline substances. She weighed 123 kg (271 lb), her pulse was 82 per minute, and her blood pressure 170/110 of mercury. She had a round face, but her fat distribution was otherwise normal. Proximal muscle weakness was evident. The rest of the physical examination elicited no abnormalities.

On admission, the urine had 2% glucose, "large ketones," and a pH of 6. Her initial blood studies showed the following: hematocrit 48%; leukocyte count 10,700 per μl; serum glucose 455, blood urea nitrogen 22, and creatinine

(Zonszein J, Baylor P: Diabetic ketoacidosis with alkalemia—A review. West J Med 1988 Aug; 149:217-219)

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1.7 mg per dl; sodium 139, potassium 2.1, chloride 80 and bicarbonate 45 mEq per liter. Arterial blood gas determinations showed a pH of 7.55, a partial carbon dioxide pressure of 43 torr, and a partial oxygen pressure of 60 torr. Serum diluted 1:8 had a positive Acetest reaction.

The hyperglycemia was easily controlled by fluid replacement and insulin therapy. The serum potassium level failed to rise above 3.5 to 4.0 mEq per liter in spite of the daily administration of 160 mmol of potassium chloride.

Cushing's syndrome was suspected because of the hypertension, diabetes, facial rounding, and the metabolic alkalosis. An overnight dexamethasone suppression test yielded a serum cortisol level of 42 μg per dl the following morning. That led to a standard conventional adrenal suppression test; the basal serum cortisol concentrations were in the range of 50 to 60 μg per dl, with urinary free cortisol in the range of 2,000 μg per 24 hours (normal 20 to 90). There was no suppressibility during the administration of either low doses (2 mg a day) or high doses (8 mg a day) of dexamethasone. Other basal hormonal levels were as follows: adrenocorticotropic hormone, less than 40 pg per dl; dehydroepiandrosterone, 50 μg per dl (normal 60 to 230); and 11-deoxycorticosterone, 27 ng per dl (normal 2 to 13). Plasma renin activity and serum aldosterone determinations made with the patient on a low-sodium diet and in an upright position were 1.0 ng per ml per hour (normal 1.5 to 5.4) and 51.0 ng per dl (normal 17 to 137), respectively.

A radiologic evaluation disclosed a normal chest and normal sella turcica. A computed tomographic (CT) scan (General Electric Model CT 8800) of the abdomen showed a 2-cm left adrenal mass and a normal-sized right adrenal gland.

After the foregoing studies were completed, the patient had rapidly worsening obstructive jaundice. A second CT scan taken five days after the first showed free retroperitoneal air. Subsequent upper and lower gastrointestinal endoscopies failed to reveal the site of presumed perforation. Endoscopic retrograde cholangiopancreatography disclosed no extrahepatic obstruction or site of perforation.

Owing to the patient's precarious condition and our failure to locate the lesion responsible for the free retroperitoneal air, it was decided to treat her medically. A cardiorespiratory arrest occurred, resuscitation was unsuccessful, and permission for an autopsy was denied.

Discussion

In patients with diabetic ketoacidosis and acidemia, there are often conditions such as vomiting, diuretic use, dehydration, and hyperventilation that cause some degree of alkalosis. Nevertheless, acidosis is the predominant disorder for most patients with severe diabetic ketosis who present with a low blood pH or acidemia. Patients in whom the acidosis is mild and disorders responsible for alkalosis predominate have the syndrome of diabetic ketoacidosis with alkalemia.[1-15] In most patients thus far described, vomiting and glycosuric osmotic diuresis resulted in dehydration and the development of secondary hyperaldosteronism. In the case here described, there was no evidence of hypovolemia and

TABLE 1.—*Laboratory Data in Patients Who Have Diabetic Ketoacidosis With Alkalemia and the Mean Values of Patients Who Have Diabetic Ketoacidosis With Acidemia*

Patient	Reference	Glucose, mg/dl*	BUN, mg/dl†	HCO_3^- (mmol/liter)	Na^+ (mmol/liter)	K^+ (mmol/liter)	Cl^- (mmol/liter)	Arterial pH	Pco_2, torr	Anion Gap, mEq/liter‡	Precipitating Factors
1	Bleicher, 1967[1]	900	NA	34	134	5.1	80	7.44	NA	25	Vomiting, alkali ingestion
2	Roggin et al, 1970[2]	984	92	45	119	4.3	40	7.59	48	38	Vomiting
3	Jiminez et al, 1975[3]	294	40	49	147	2.5	74	7.57	NA	26	Vomiting
4	Lim and Walsh, 1976[4]	342	48	34	135	3.8	NA	7.55	41	NA	Vomiting
5	Lim and Walsh, 1976[4]	234	66	30	140	4.5	NA	7.60	38	NA	Vomiting
6	Lim and Walsh, 1976[4]	549	69	30	129	4.2	NA	7.50	41	NA	Vomiting, alkali ingestion
7	Melrose et al, 1976[5]	636	130	29	139	3.9	NA	7.53	27	NA	Vomiting
8	Shirley and Martin, 1976[6]	476	NA	30	NA	NA	NA	7.47	42	NA	None
9	Sanders et al, 1978[7]	648	9	42	140	0.8	69	7.55	56	30	Vomiting, diarrhea
10	Koett et al, 1979[8]	958	65	38	123	2.5	56	7.66	23	32	Diuretic use, hyperventilation
11	Fulop, 1980[9]	NA	NA	29	140	4.1	97	7.58	32	18	Vomiting
12	Fulop, 1980[9]	NA	62	21	142	3.9	98	7.46	31	27	Hyperosmolar coma
13	Fulop, 1980[9]	NA	NA	23	135	3.2	90	7.52	30	25	Diuretic use, hyperosmolar coma
14	Pearson et al, 1981[10]	405	29	40	NA	1.8	NA	7.61	34	NA	Hypercortisolism, diuretic use
15	Cronin et al, 1984[11]	1,047	NA	30	127	4.1	78	7.70	11	23	Diuretic use
16	Prando et al, 1984[12]	529	NA	56	144	3.4	77	7.56	62	14	Vomiting
17	Capps et al, 1986[13]	900	53	18	135	3.0	70	7.52	19	50	Vomiting, diuretic use
18	O'Reilly and Delamere, 1980[14]	702	36	27	NA	2.1	NA	7.52	32	NA	Hypercortisolism, lung mass, diuretic use
19	Greco et al, 1985[15]	257	14	19	142	4.0	100	7.48	26	27	Hyperventilation, elevated stress hormones, alkali ingestion
20	This report	455	22	45	139	2.1	80	7.55	43	16	Hypercortisolism, diuretic use
	Mean values	606	52	33	136	3.3	78	7.55	35	27	
	Mean values in acidemia§	589	27	6	132	5.7	98	7.06	20	33	

BUN=blood urea nitrogen, Cl^-=chloride, HCO_3^-=serum bicarbonate, K^+=potassium, Na^+=sodium, NA=not available, Pco_2=partial pressure of carbon dioxide

*To convert to millimoles per liter, multiply by 0.05551.
†To convert to millimoles per liter, multiply by 0.357.
‡Calculated as $(Na^+ + K^+) - (Cl^- + HCO_3^-)$ = mEq/liter.
§Adapted from Adrogué, 73 patients with 196 events of acidemia ketoacidosis.[16]

the electrolyte abnormalities appeared to be due to the mineralocorticoid effect of the high cortisol levels as well as their antianabolic effects.

In comparing the biochemical abnormalities of patients with diabetic ketoacidosis and alkalemia (Table 1) and those of patients with diabetic ketoacidosis and acidemia,[16] differences are found that imply distinct pathogenetic abnormalities. The patients with alkalemia tended to be more dehydrated than those with acidemia, as reflected by the differences in blood urea nitrogen concentrations. Plasma ketoacid concentrations were determined in only three patients with alkalemia in studies by Fulop,[9] which showed a mean plasma β-hydroxybutyrate of 3.1 mmol per liter, in contrast to a mean plasma concentration of β-hydroxybutyrate of 22.1 mmol per liter in the acidemic group.[16] Both groups of patients had similar elevations in the anion gap. Clues to the presence of "masked acidosis" in patients with a high pH include the presence of ketonemia and ketonuria and a high anion gap.

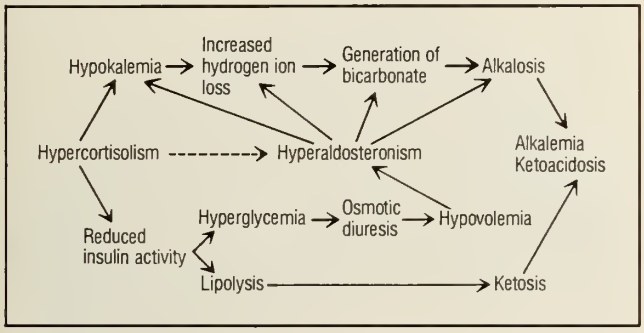

Figure 1.—The diagram shows postulated pathogenetic mechanisms for the development of diabetic ketoacidosis with alkalemia.

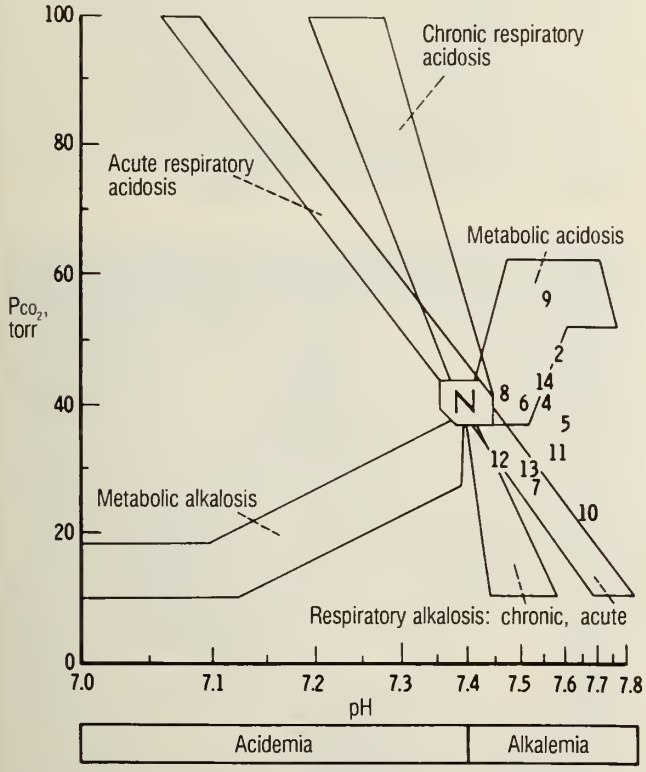

Figure 2.—The graph shows arterial blood pH and carbon dioxide tension (Pco_2) in 12 patients with diabetic ketoacidosis with alkalemia. The numbers correspond to patients' numbers in Table 1. Note the terms acidemia and alkalemia reflecting only changes in pH. N = normal

In patients with diabetic ketoacidosis and alkalemia, the metabolic acidosis is masked by alkalemia where the mean pH in the reported patients was 7.55 (Table 1). Alkalemia has been shown to increase the anionic equivalence of serum proteins, particularly albumin. Further, dehydration, a common feature of most ketoacidotic or alkalotic states, can also increase the anion gap by increasing the serum protein concentration. The significance of these effects, however, appears to be minimal. In analyzing the biochemical abnormalities in 12 patients with metabolic acidosis and alkalemia, Fulop found that the increased anion gap in these patients with a mixed acid-base disturbance was caused mainly by the coexisting elevated keto or lactic acids.[9]

Therapy for diabetic ketoacidosis with alkalemia does not differ greatly from the usual treatment of ketoacidosis with acidemia. Potassium should be administered early. Bicarbonate administration is contraindicated. Insulin requirements may be modest, and proper fluid replacement is of paramount importance.

Diabetic ketoacidosis and alkalemia illustrate the complexity of acid-base imbalance. When diabetic ketoacidosis is accompanied by alkalemia, the common predisposing factors such as vomiting, alkali ingestion, or diuretic therapy must be identified. If these are not found, we recommend considering the possibility that hypercortisolism or hyperaldosteronism may be present. When hypercortisolism is identified, it is often associated with a fulminating illness (Figure 1). In the two previous cases reported[10,14] and the present case, death followed within weeks of presentation. We think that the incidence of diabetic ketoalkalosis has been underestimated because most series of diabetic ketoacidosis exclude those with a pH of 7.40 or higher, and only those with a pH of 7.45 or above have been reported as having diabetic ketoacidosis with alkalemia (Figure 2).

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Trichobezoar Associated With Gastric Polyposis

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TRICHOBEZOARS AND PHYTOBEZOARS are the most common types of bezoars seen in humans. In a comprehensive review of the literature, DeBakey and Ochsner reported 171 cases of trichobezoar, 119 cases of phytobezoar, and 13 cases of other concretions.[1]

Trichobezoars are composed of hair, mucus, and undigested fat. They are seen most often in otherwise healthy young girls with trichophagia. In contrast, phytobezoars occur in patients with abnormalities of the gastrointestinal tract and are composed of undigested plant material.[1] Predisposing conditions for phytobezoar formation include postgastrectomy states, diabetic gastroparesis, and absent teeth.[1-3]

Reported complications of bezoars include ulcers, perforation, gastric outlet obstruction, and intestinal obstruction.[1] These problems presumably develop on a mechanical basis. Iron deficiency[1,4-7] and megaloblastic anemias[8] have also been reported in patients with bezoars.

The rare association between bezoars and gastric polyposis is less well appreciated. In fact, while the aforementioned review of 303 cases noted that ulcer, perforation, obstruction, and anemia were frequent complications of bezoars, polyposis was not mentioned.[1] We recently saw an unusual case of a patient with a large trichobezoar and extensive polyposis of the stomach and duodenum. Her case history and histologic findings are presented, and the literature regarding bezoar associated with gastric polyposis is reviewed.

Report of a Case

The patient, a 17-year-old girl, was evaluated at the Oregon Health Sciences University for nausea and epigastric pain. Her pain had been present intermittently for many years but had worsened three weeks before the evaluation. Abdominal pain was maximal in the epigastric region and was not associated with eating or activity. She had occasional nausea after eating large meals but no vomiting. She said she did not have anorexia but had lost 4.5 kg (10 lb) over the previous three weeks. She complained of weakness, dizziness, and easy fatigability. She said she did not have melena or lower gastrointestinal symptoms, including rectal bleeding. Her menses were normal with menarche at age 12.

Her medical history was unremarkable. A social history revealed a disruptive family background with parental divorce, and she had abused alcohol around the time of the divorce. At the time of evaluation, she was living with her mother and attending high school. She said she did not abuse drugs.

On physical examination, she was pale but in no distress. Her blood pressure was 110/75 mm of mercury, and her pulse rate was 100 per minute; she was afebrile. Her height was 155 cm (61 in) and weight 48 kg (105 lb). Conjunctivae were pale. The cardiac examination revealed a I/VI systolic ejection murmur at the base without radiation. The abdomen was soft with normal bowel sounds and no masses. The liver was 10 cm in span and was not palpable. There was slight tenderness in the left upper quadrant and epigastrium without guarding or rebound. A rectal examination showed brown stool negative for occult blood. A pelvic examination showed no abnormalities. There was mild ankle edema.

A laboratory evaluation elicited the following: hemoglobin, 6.0 grams per dl; hematocrit, 21.5%; mean corpuscular volume, 59 cu microns; mean corpuscular hemoglobin concentration, 28 grams per dl; red cell distribution width, 20.3%; leukocyte count, 7,500 per μl; platelet count, 764,000 per μl; reticulocyte count, 2.2%; and erythrocyte sedimentation rate, 10 mm per hour. Serum electrolyte and liver test values were normal. A serum albumin level was 2.9 and total protein 4.7 grams per dl; calcium 8.2, phosphorus 5.0, and uric acid 2.0 mg per dl. The serum iron level was 2 μg per dl, iron binding capacity 267 μg per dl, and serum ferritin <5.0 ng per ml. The results of hemoglobin electrophoresis and a urinalysis were normal, as was an electrocardiogram.

An upper gastrointestinal series revealed two large intraluminal filling defects, hypertrophied mucosal folds, and an ulcer on the lesser curvature of the stomach. Panendoscopy showed a large trichobezoar extending into the duodenum. There were multiple polyps too numerous to count, ranging in size from 2 mm to 2 cm, and extending from the body of the stomach to the second portion of the duodenum (Figure 1). A 1-cm ulcer was present on the lesser curvature of the stomach. Biopsy specimens of the polypoid masses showed fragments of normal duodenal and gastric mucosa, and a biopsy of the gastric ulcer was unremarkable.

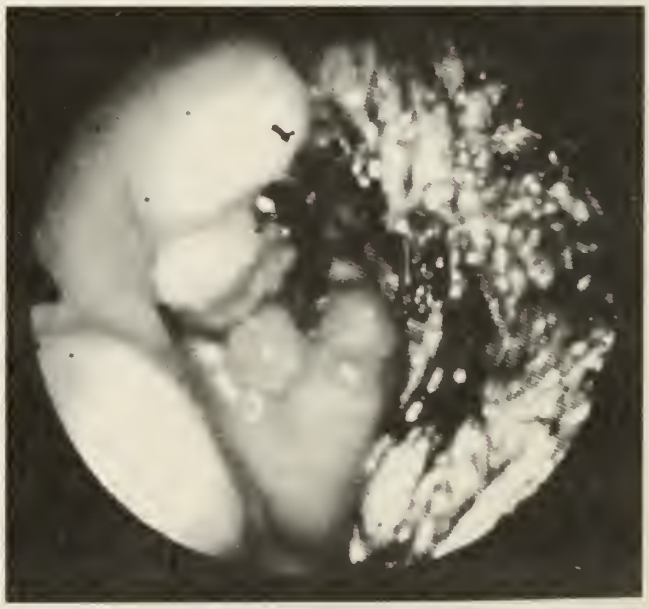

Figure 1.—An endoscopic photograph shows a trichobezoar on the right and multiple gastric polyps on the left.

(Bates CK, Keeffe EB, Sahin A: Trichobezoar associated with gastric polyposis. West J Med 1988 Aug; 149:220-223)

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On further questioning, her mother gave a history of hair ingestion by the patient since age 2 to 4 years. The patient remembered pulling on the ends of her hair as a small child but thought she had stopped this habit at age 12.

She was admitted to hospital, transfused with three units of packed red cells, and given parenteral nutrition. An exploratory laparotomy with gastrotomy was done and the trichobezoar extracted (Figure 2). Excisional biopsy specimens of several polyps showed hyperplastic glands and a fibrous stroma (Figures 3 and 4). There were no adenomatous features in any of the polyps. Her recovery was complicated by a wound abscess that resolved with drainage and antibiotic therapy.

She returned to school and experienced a dramatic increase in energy. Her appetite improved, and she gained 11 kg (25 lb) over three months. Her hematocrit was normal two months following the operation. A follow-up endoscopy three months after the operation showed no intraluminal hair or bezoar and healing of the previous gastric ulceration. The body and antrum of the stomach and proximal duodenum contained scattered polyps ranging from 2 mm to 10 mm in diameter. The polyps appeared somewhat decreased in size and number compared with her original endoscopy.

The patient underwent a repeat evaluation 18 months after the surgical excision. She remained well without any gastrointestinal symptoms and gained an additional 11 kg (25 lb) in body weight to 71 kg (157 lb). The results of a complete blood count and chemistry panel were normal with a hematocrit of 43.9% and a serum albumin level of 4.6 grams per dl. A follow-up endoscopy showed persistent polyps scattered from the mid-body of the stomach to the proximal second portion of the duodenum. The polyps were strikingly decreased in size to 1 to 4 mm in diameter and in number to 20 to 30 lesions in the stomach and 10 to 12 in the duodenum. Biopsy specimens of both gastric and duodenal polyps showed a normal surface epithelium with resolution of the previous hyperplasia but persistent fibrosis in the lamina propria.

Figure 2.—The photograph shows a trichobezoar, formed in the shape of the stomach, after removal by gastrotomy.

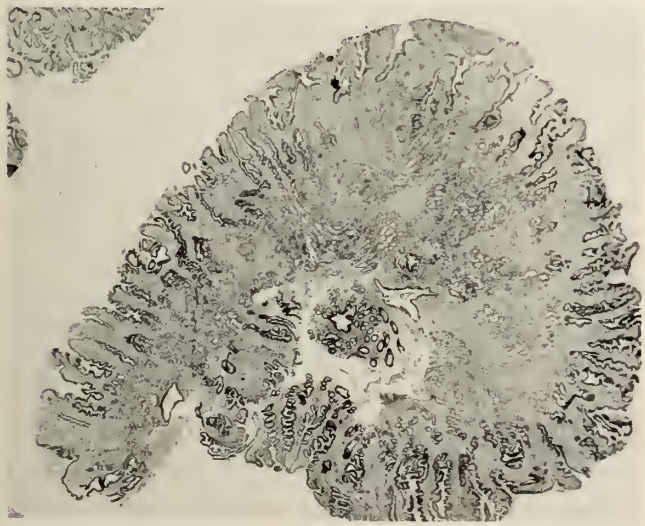

Figure 3.—A low-power view of a hyperplastic gastric polyp shows elongated and tortuous foveolae separated by fibrous stroma and smooth muscle bundles (original magnification × 23).

Discussion

An association between bezoars and gastric polyposis was first recognized in 1921[9] but has been noted in only a few subsequent case reports (Table 1). Davies reported the case of a patient with a trichobezoar and a large papilloma on the lesser curvature of the stomach with several similar smaller tumors in the antrum. The polyps were resected, but the

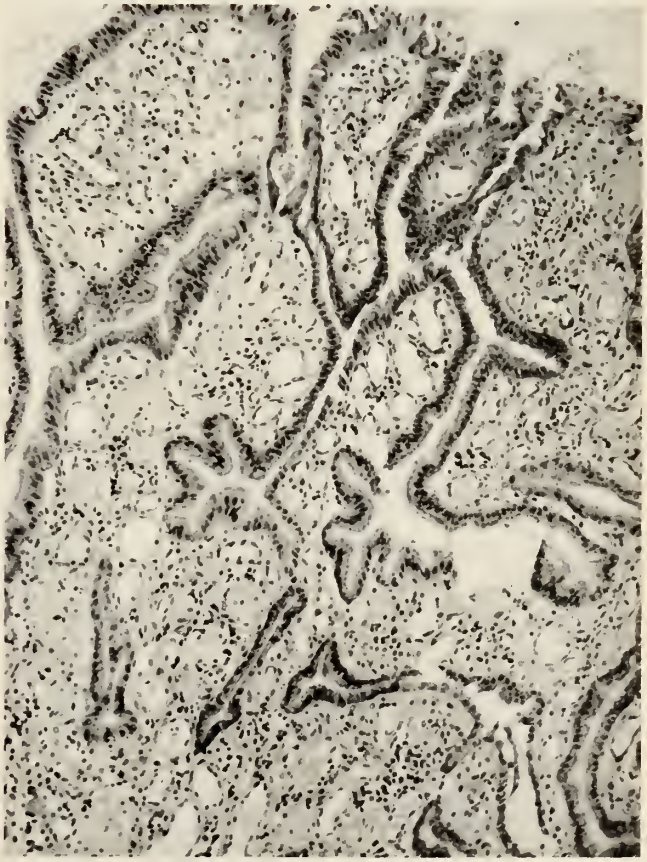

Figure 4.—A high-power view of hyperplastic foveolae and stroma shows prominent vascular structures (original magnification × 150).

TABLE 1.—*Patients With Trichobezoar and Gastric or Gastroduodenal Polyposis*

Source	Location and Number of Polyps	Gastric Ulcers	Serum Albumin Level, grams/dl	Serum Hemoglobin Level, grams/dl
Davies, 1921[9]	Distal stomach; multiple	Absent	?	?
Charache et al, 1957[10]	Distal stomach; multiple	Absent	Normal	Normal
Valberg et al, 1966[4]	Stomach; nodularity only	Absent	1.4	8.9
Hossenbocus and Colin-Jones, 1973[11]	Distal stomach and duodenum; 2	Surface of polyp	1.3	10.9
This report	Distal stomach and duodenum; multiple	Lesser curvature	2.9	6.0

histologic examination of these lesions was not reported. Hyperplasia of the gastric mucosa of patients with bezoars was later noted,[1] but a relationship between bezoars and polyposis was not reported again until 1957, in a patient who also had apparent premalignant change in a polyp.[10] This patient underwent a subtotal gastrectomy after an earlier gastrotomy, and excision of a polyp showed "incipient malignant degeneration." Pathologic analysis of the remaining multiple polyps in the distal two thirds of the stomach showed no evidence of malignancy.

An association between trichobezoars and a hypertrophic gastric mucosa, edema, hypoalbuminemia, and protein-losing gastroenteropathy was postulated by Valberg and coworkers on the basis of a report of two patients with documented protein loss in stool.[4] The gastric mucosa was thickened in both patients and grossly nodular in one of the patients. A histologic analysis of a specimen of gastric mucosa from the latter patient showed hyperplasia of the surface epithelium with elongation and tortuosity of the foveolae, which gave a polypoid appearance in some areas. Hossenbocus and Colin-Jones expanded the association between trichobezoar and protein-losing gastroenteropathy with hypoalbuminemia and edema to include gastric polyposis.[11] Protein loss was documented by measuring radiolabeled protein excretion in feces. Their patient had numerous gastric polyps and two small duodenal polyps, all of which were histologically benign. A repeat evaluation by endoscopy two months following a laparotomy showed resolution of the edema and a decrease in the size of the polyps.

Our patient had more extensive polyposis than the patients in the few cases noted above. Polyps were seen throughout the body of the stomach and extended into the second portion of the duodenum as far as the length of the bezoar. They ranged in size up to 2 cm and were too numerous to count. She had moderate hypoalbuminemia and edema in the absence of proteinuria, and, therefore, likely had protein-losing gastroenteropathy. The 18-month follow-up endoscopic examination of our patient provides new information on the natural history of gastroduodenal polyposis associated with the presence of a bezoar. The pronounced decrease in polyp size and number suggests that hyperplastic polyps are likely to gradually resolve, although residual fibrosis in the lamina propria may result in a persistence of some polypoid lesions. The reduction in polyp size and number and the absence of lower gastrointestinal symptoms rule against gastric polyposis associated with familial polyposis coli.

Our patient also had iron deficiency anemia. Reviewing the literature regarding bezoars reveals that anemia is not correlated with the presence of either gastric polyposis or ulceration.[5-7] One report even postulates that trichophagia may be due to pica associated with iron deficiency, and, thus, trichobezoars may be a consequence rather than a cause of anemia.[7]

The explanation for the association between gastric polyps and bezoars remains speculative. Polyps have been associated only with trichobezoars and not with phytobezoars. One proposed mechanism of polyp formation is abrasion and secondary inflammation of the surface mucosa.[11] The correlation in our patient with the length of the bezoar and the extent of mucosa exhibiting polyposis as well as the decrease in polyp number and size after the bezoar was removed supports the role of mucosal abrasion in polyp formation. It is difficult to explain, however, why polyps have been noted only rarely in patients with trichobezoars. The size of the bezoar is also apparently not related to the development of polyposis. Patients have been noted to have massive bezoars that formed a cast of the distended stomach whose mucosa remained normal.[6] Polyp formation does not appear to be related to the length of a bezoar in the gastrointestinal tract. One patient with a 120-cm long bezoar extending from the stomach to the transverse colon had mucosal ulcers but no polyps.[5] On the basis of the theory of abrasion with a secondary inflammatory reaction, it seems reasonable to postulate an association between polyps and chronicity of a bezoar, but this is difficult to prove. Our case is representative of others cited in the literature with trichophagia and hair in the stool for many years preceding the diagnosis of trichobezoar, and yet most of the patients did not have polyps.[1] The 15-year history of trichophagia in our patient is particularly long, however, and a trichobezoar causing mucosal abrasion may have been present long enough to result in gastroduodenal polyposis.

It is possible that polyposis preceded the formation of trichobezoars in the few reported cases in which both conditions are present. The incidence of bezoar formation in patients with trichophagia is unknown. It has been postulated that hair may not be propelled normally through the stomach but trapped in mucosal folds.[1,10] Although gastric and duodenal polyps are rare, their antecedent presence in a patient with trichophagia might facilitate hair entrapment and bezoar formation.

In summary, this female adolescent with trichophagia had several of the complications reported in patients with trichobezoars, including iron deficiency anemia, hypoalbuminemia, and gastric ulcer. She also had the rare association of trichobezoar and benign gastric and duodenal polyposis as an additional complication. The presumed causality between bezoars and polyposis remains speculative, but polyposis probably results from chronic abrasion of the gastric mucosa leading to a secondary inflammatory and a hyperplastic response with polyp formation. The gradual decrease in the size and number of polyps in our patient after the bezoar was removed supports this hypothesis.

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Fatal Pneumonia Caused by Parainfluenza Type 3 Virus

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MANIFESTATIONS OF MORBIDITY subsequent to parainfluenza virus infections in infants have recently been reported by McCarthy and co-workers.[1] Potential mortality from severe lower respiratory tract infections due to these organisms must also be considered.

From June 1986 through January 1987, parainfluenza virus type 3 was identified in respiratory tract specimens of 29 patients with symptoms of clinical disease at Childrens Hospital of Los Angeles (CHLA). During this interval, two infants younger than 3 months and previously healthy died as a result of severe injury of the lower respiratory tract presumably by this viral agent.

Reports of Cases

Case 1

The patient, a 6-week-old female infant, presented to the CHLA emergency department with rhinorrhea, cough, and congestion for one week. She was noted to be in moderate respiratory distress, and a chest x-ray film showed bilateral pneumonitis. The patient then became apneic, requiring the insertion of an endotracheal tube. Despite increased ventilatory support and the parenteral administration of ampicillin and gentamicin sulfate, she died of respiratory failure on the 15th day. Cultures of specimens of blood, cerebrospinal fluid, urine, stool, and tracheal aspirate were reported as negative for bacteria. Cultures for respiratory syncytial virus, cytomegalovirus, and *Chlamydia trachomatis* were also negative. An endotracheal tube aspirate obtained on the second hospital day and inoculated into rhesus monkey kidney cells yielded after 14 days parainfluenza virus type 3.

(Ross LA, Hitchcock W: Fatal pneumonia caused by parainfluenza type 3 virus. West J Med 1988 Aug; 149:223)

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A request for a postmortem examination was denied by the family.

Case 2

The patient, a 3-month-old female infant, was seen in the CHLA emergency department with fever and respiratory distress. A septic workup was done and therapy begun with ampicillin and chloramphenicol sodium succinate. A chest x-ray film showed bilateral interstitial pneumonitis. On the fourth hospital day, increasing respiratory distress developed, and the patient required the insertion of an endotracheal tube. Despite respiratory support, her pulmonary status deteriorated, and she died on the seventh hospital day. Cultures of specimens of blood, cerebrospinal fluid, urine, and endotracheal aspirate were negative for bacteria. Specimens from nasopharynx and endotracheal tube obtained on the fourth hospital day yielded parainfluenza virus type 3, twelve days after being inoculated into rhesus monkey kidney cells.

On postmortem examination, there was extensive interstitial pneumonitis, and cultures of specimens of lung were positive for parainfluenza type 3. In addition, acute bronchopneumonia with lung cultures positive for *Pseudomonas aeruginosa* was identified. A histopathologic evaluation did not suggest the presence of a congenital immune deficiency or an underlying cardiac abnormality.

Discussion

While parainfluenza virus type 3 is recognized as an important cause of lower respiratory tract disease, there were no deaths in the series reported by McCarthy and associates.[1] Our report indicates that parainfluenza type 3 can cause fatal lower respiratory tract disease in previously healthy infants. While the presence of an immunologic, cardiac, or pulmonary disorder cannot be entirely excluded in case 1, a complete postmortem examination in case 2 did not reveal such preexisting abnormalities.

Although the sensitivity of rapid diagnostic techniques to detect respiratory syncytial virus is considered to be at least 90%, a recent report indicates that rapid diagnostic tests to detect parainfluenza type 3 virus show poor sensitivity.[2] In addition, isolating parainfluenza viruses may require an average of more than six days,[3] which lessens the clinical impact of identifying the agent. A modification of cell culture screening methods[4] may substantially shorten the detection time.

The optimal care of infants with severe lower respiratory tract infections caused by parainfluenza viruses includes aggressive supportive measures. The availability of diagnostic techniques for detecting parainfluenza virus with enhanced sensitivity and acceptable degrees of specificity would permit the consideration of additional therapeutic methods such as the use of ribavirin[5] and the intravenous administration of immune globulin.[6]

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Correspondence

Cost-Effectiveness of Coronary Care

To THE EDITOR: It was with a profound sense of déjà vu that I read Murata's article[1] and Goldman's editorial[2] in the May issue recommending that, as a cost-saving measure, patients with chest pain who are at low risk for myocardial infarction (MI) be treated in an intermediate rather than an intensive coronary care unit (CCU). That discussions of this type continue to take place 25 years after coronary care units were first introduced seems little short of extraordinary and demands additional explanation.

It was always clear that clinical risk in the context of potential and actual myocardial infarction varies widely. This concept was incorporated into the design and operation of one of the earliest CCUs in California. At the Peninsula Hospital in Burlingame, patient triage has been used since 1965 to match intensity of care to anticipated risk. Remote monitoring was provided to low-risk patients in a minimally altered hospital wing, while more critical patients were treated under direct vision in an intensive care unit-type environment.

The efficient use of resources was designed to permit longer periods of monitoring than the 48 hours that were considered standard at the time. In a deliberate attempt at economy, 11 remotely monitored beds were installed at a cost of $29,900. Adding only 50 cents per hour to the normal daily hospital room rate covered both installation and operating expenses and amortized the cost of equipment. Even in 1964, this was a bargain.

In keeping with the experience at other institutions, in-hospital myocardial infarction mortality rates at the Peninsula Hospital fell from 26% to 15%. These results were achieved even though the vast bulk of care from admission to discharge was provided in the less intensive unit.[3] Still, this approach was eventually abandoned in favor of more expensive full-bore treatment for all suspected MI patients. Why? For a variety of extraneous reasons, which have militated against greater economic efficiency in coronary care at Peninsula Hospital and, I suspect, at virtually all institutions.

Most important, the enactment of Title 22 of the California health code eliminated local option in CCU design. Private rooms of a specific size and with specific equipment were mandated by law in an effort to improve and codify standards. Anything less no longer qualified as a bona fide CCU. This had intensely practical consequences, since Medicare and other insurers stopped paying any surcharge above basic day rates for care rendered in non-qualifying facilities.

Nor in the example given above did the surcharge long remain at 50 cents per hour. Hospital rates are set by accountants who compare local charges with those of other institutions. Higher charges elsewhere offer an opportunity to raise rates with little fear of criticism. Physicians are not generally welcome if they object to the conversion of an inexpensive CCU into a profit center.

For those physicians interested in cost-effective coronary care, no constituency for keeping things simple was to be found. The focus at clinical meetings lay elsewhere. Cardiology itself evolved into a more complex and invasive specialty, and the continuous upgrading of facilities and services seemed to have a momentum of its own. Rivalry with other institutions and local prestige factors may also have played a role, affecting nurses as well as physicians. Subspecialty care, with its inherent bias toward complexity, has made progressive inroads into the cardiologic portion of the practices of general internists and other primary physicians, even with low-risk patients.

In short, it has always been reasonable to treat low-risk suspected myocardial infarction patients in an intermediate rather than an intensive CCU. But there remain important socioeconomic, regulatory, and professional obstacles to doing so.

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Experience of a 'Dirtball' Patient at a University Hospital

To THE EDITOR: It has been over half a decade since Cato 6 eloquently reminded us of the inappropriateness of the term "dirtball" when applied to a patient.[1] While most caregivers refrain from using such nouns, their expressions and actions may make the patient feel like a "dirtball." I was recently unfortunate enough to require emergency treatment at a local university hospital. There was a profound and unpleasant difference between the treatment I got from those who knew me as a medical student and those who only saw me as I presented.

While bodysurfing, I received a flexion injury to the neck, resulting in severe pain that radiated down my right arm. I was told to lie still in the sand as the paramedics tied me to the spineboard and prepared to transfer me to hospital. Now, imagine if you will what I must have looked like coming into the emergency room on a Friday night: a man with a five o'clock shadow, dressed only in tattered shorts, wet, hair and body matted with dirt and sand, and tied to a spineboard. While the intern—who happened to be a good friend—proceeded with a thorough neurologic examination, the nurse exclaimed in an extremely annoyed voice (as if I couldn't hear), "Oh my god . . . this guy's getting dirt all over the place." Next, the same professor who had given me superior marks on my surgery oral exams the month before did not recognize me and gave me a look and a shake of the head that seemed to say, "Oh no . . . another dirtball." In each section of the hospital, those who knew me rolled out the red carpet and those who didn't had "dirtball" in both their expressions and actions. While sitting in the emergency room with some of the other "dirtballs," I couldn't help but think how miserable it must be to be treated like this all the time.

Luckily, I emerged from the incident with no permanent injury. Now, when I care for unpleasant or even hateful patients, I make an extra effort in both my words and actions to

let them know that I care and will work my hardest to help them. We must remember that no matter how dirty, smelly, unpleasant, or hateful patients are, they have come to us because they are in need. And that dirtball might just be the medical student who rotates through the emergency room next month.

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Deficiencies in Soviet Medicine

To THE EDITOR: Having read the letter from Drs Rafferty and Schultz[1] commenting on Friedenberg's article on the Soviet health care system,[2] I was encouraged to re-read that article. I had the pleasure and honor of following Drs Rafferty and Schultz as an exhibit physician into Tbilisi, Soviet Georgia, for two months; they had served at Kiev and Rostov.

I, too, feel that Dr Friedenberg is unnecessarily kind in his assessment of Soviet medical care and, in some instances, in error.

The examples of deficiencies in Soviet medicine are too numerous to mention in a letter, and in this sense they reflect exactly what is going on in the rest of Soviet society. It may be simpler just to say that in no respect does their system, in its philosophy or execution, serve as a model for anyone else's. Nor, at this time, are its foundations or accomplishments sufficient to be the basis for improvement. Just as the rest of their society has stagnated, so has their health care system.

It may very well be, as Drs Rafferty and Schultz point out, that Soviet health expenditures are 2% of their gross national product. The real cost in mortality and morbidity and the unmeasured cost and effort of trying to circumvent the system to obtain decent care could easily push that figure into double digits, however.

We must help our Soviet colleagues in every way we can. This cannot be accomplished until the *glasnost*, which is the essence of scientific intercourse, is allowed to permeate this until now impenetrable border, mind and soul. This effort is not at all abetted by abrogating our usual high standards of criticism, which began with the Flexner report. Would that it were applied to Soviet medicine.

Dr Friedenberg is doing a disservice to our Soviet brethren by permitting them to compare their present standards to their past accomplishments and not to present-day western ones. Even by their own standards, they have regressed. Free care is the hubris on which the Soviets base their criticism of our system. For Dr Friedenberg to grab their banner, knowing full well the real cost of free care, is to gloss over the failure of the system, which has done very little in 70 years except to remain nominally free.

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Topics in Primary Care Medicine

The Lumpy Breast

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Lumps in the breast are common—in as many as 50% of premenopausal women, breast lumps are found on careful physical examination. Most of these lumps are benign, but the fact that breast cancer is in the differential diagnosis may require breast imaging and tissue sampling. If breast lumps are benign, a physician must decide if the woman has an increased risk of breast cancer developing, if screening for breast cancer should be more frequent or more intense, and if any treatment is necessary.

Definitions

The terms used by clinicians, radiologists, and pathologists to describe breast masses are often confusing. To avoid this problem, we will begin with several definitions. "Breast lumps" are masses in the breast noted on physical examination that may be either benign or malignant. "Benign breast disease" includes any breast lesion that is not malignant. Various findings on history, physical examination, and breast imaging may support the diagnosis of benign disease, but, strictly speaking, benign breast disease is a pathologic definition and should be applied only to masses that have undergone tissue sampling. It is a heterogeneous group of lesions, including fibrocystic disease, fibroadenoma, and other uncommon conditions such as mastitis, lipoma, traumatic fat necrosis, and galactocele. At biopsy, 90% to 95% of all benign breast disease is fibrocystic disease or fibroadenoma.

"Fibrocystic disease" is an ill-defined group of pathologic breast lesions, including cysts, fibrosis, adenosis, duct ectasia, hyperplasia, and papilloma. The incidence of fibrocystic disease increases with age, peaks at about the time of menopause, and then declines. Clinically, women with fibrocystic disease often have multiple tender nodules that are symmetrically distributed in both breasts. The nodules typically increase in size and become more painful just before the menses. Some forms of fibrocystic disease cause a solitary mass. Occasionally no palpable mass is evident, and the diagnosis is noted incidentally at biopsy or autopsy.

"Fibroadenoma" is another pathologic type of benign breast tumor. It is common in women younger than 30 years and becomes less common with increasing age. It usually presents as a solitary, firm, rubbery, smooth, and mobile mass. Findings on history, physical examination, or mammogram may suggest fibrocystic disease or fibroadenoma, but these terms should be used only as pathologic diagnoses.

Epidemiology

As many as 50% of premenopausal women have breast lumps noted on a careful physical examination, and as many as 89% of postmenopausal women have pathologic evidence of benign breast disease at autopsy. Among women younger than 30 with benign breast disease, fibrocystic disease and fibroadenoma are about equally represented, each accounting for about 45% of cases. In women older than 30, about 85% of cases are fibrocystic disease and only 10% are fibroadenoma. In some studies, these two conditions are more common in women who are white, of upper socioeconomic status, and obese. These factors may reflect better access to medical care in white upper-class women and more difficulty in detecting lumps in obese women. Classic risk factors for breast cancer—personal or family history of breast cancer, early menarche, late menopause, and nulliparity—are not clearly associated with benign breast disease. A lower incidence of the disease in women who use oral contraceptive pills has consistently been reported, but this may reflect the fact that many physicians hesitate to initiate such therapy in women with breast lumps.

Clinical Evaluation

The main objective of a clinical examination is to decide if breast lumps are suggestive of breast cancer. If a lump has been noted by the patient, she should be asked how long it has been present, if it waxes and wanes with the menstrual cycle, and if there is associated cyclic tenderness. Nodules that have been present and unchanged for more than a year are usually benign, and cyclic symptoms suggest benign disease. Risk factors for breast cancer, including a previous history of breast cancer, a family history of breast cancer, and increasing age, should be reviewed, as well as symptoms of breast cancer such as fatigue, weight loss, and bone pain.

The proper performance of a breast examination should

(Grady D, Hodgkins ML, Goodson WH III: The lumpy breast. West J Med 1988 Aug; 149:226-229)

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include inspection and palpation of the breast, an attempt to express nipple fluid, and palpation of the lymph nodes. An examination should always be done, or repeated, at seven to ten days into the menstrual cycle because some suggestive masses noted just before the menses will regress or disappear as hormonal stimulation of the breast decreases.

Physical findings should be categorized as benign or suggestive of breast cancer. On inspection, skin dimpling, a spontaneous nipple discharge, or asymmetry of the breasts is suggestive. On palpation, benign breast lumps are usually multiple, bilateral, generally uniform, and symmetrically distributed, and they may be slightly tender. The sensation on palpation is similar to the feeling of sliding the fingers over a mass of peas or grapes. The consistency of the nodules may vary from firm and rubbery to fluctuant. Clinicians often label these physical findings as "fibrocystic disease," but without tissue sampling, this condition should be called "lumpy breasts." A breast lump is described as a dominant mass when the breasts are diffusely nodular but one mass is clearly larger, firmer, or asymmetric in location. Dominant masses are suggestive of breast cancer and require further evaluation. A lump is described as solitary if no other masses are present. In women younger than 25 years, solitary masses that are smooth, rubbery, and mobile are most commonly found to be fibroadenoma at biopsy, but without tissue sampling should simply be called a "solitary breast mass." "Thickening" is another descriptive term used to refer to an area of the breast that feels denser than the rest of the tissue. This most commonly occurs in the upper outer quadrant of the breasts—an area where there is more glandular tissue than in the other quadrants. If benign, thickening should be roughly symmetric.

Dominant or solitary masses that are small, soft or cystic, smooth, and movable are more likely to be benign. Conversely, masses that are hard, irregular, or fixed and asymmetrically thickened suggest breast cancer. Unfortunately, the clinical characteristics of these suspicious physical findings are not accurate enough to distinguish benign from malignant disease, and further diagnostic testing is necessary.

Diagnostic Evaluation

Routine laboratory tests are not helpful in evaluating breast nodules. Useful diagnostic procedures include mammography, fine needle aspiration, excisional biopsy, and, occasionally, echomammography.

Mammograms are usually classified as benign, malignant, or suspicious based on established radiologic characteristics. In the evaluation of a suspicious breast mass, mammography has a sensitivity of about 80% and a specificity of about 90%. About 20% of women with palpable cancer will have a mammogram that shows no evidence of cancer, and this rate may be as high as 30% in younger women with dense breasts. Mammography should be done in the evaluation of a suspicious breast mass, but a normal mammogram alone should not delay tissue sampling. A mammogram is useful to confirm the clinical suggestion of a malignant mass and especially to identify other nonpalpable suspicious areas in both breasts that might also require evaluation.

Fine needle aspiration (FNA) is a method for obtaining fluid and cellular material from a palpable mass. A fine needle (22 or 23 gauge) is inserted directly into the suspicious mass, and aspirated material is immediately smeared and fixed for cytologic examination. The procedure is no more painful than venipuncture, it is rapid—about five minutes for the patient procedure and 24 to 48 hours for the cytologic evaluation—essentially without side effects, and relatively inexpensive. The results of a cytologic examination of aspirated material are reported as malignant, benign, or suspicious. When done and interpreted by an experienced cytologist, the false-negative rate—FNA read as benign when the lesion is malignant—is about 1.4%, a level that compares favorably with frozen section (0.7% to 4.9%) and excisional biopsy (1.4%). The false-positive rate—FNA read as malignant when the lesion is benign—approaches 0%. When the aspiration, fixing, or cytologic evaluation is done by inexperienced personnel, the accuracy of the test may fall to unacceptable levels. A clinician considering using fine needle aspiration of breast lumps should check with the cytologist who evaluates the aspirates to make sure the false-positive and false-negative rates are acceptable.

In clinical settings where expert FNA and cytologic evaluation are not available, the evaluation of a suspicious mass requires excisional biopsy. The biopsy is usually done as an outpatient surgical procedure, using local anesthesia, with an attempt made to remove the entire mass. The subsequent risk status and treatment are based on the pathologic diagnosis.

At present, echomammography is not sufficiently accurate to be useful for distinguishing benign from malignant breast masses, although it reliably differentiates cystic from solid masses. Because breast cysts are invariably benign, a suggestive mass that is clearly cystic on an ultrasound study needs no further evaluation. For suggestive palpable masses, FNA is preferred because it is highly accurate in diagnosing cysts, will also provide diagnostic information if the mass is solid, and is generally less expensive than echomammography. For nonpalpable suspicious masses noted on mammography, the echomammographic diagnosis of a cyst may obviate the necessity for mammographically directed biopsy because as many as 25% of such lesions are cysts.

Figure 1 outlines a general approach for evaluating a woman with breast lumps. If the lumps are multiple, bilateral, diffuse, and symmetric, no further diagnostic testing is necessary. Examination in such women may be difficult, however, and routine monthly breast self-examination, a yearly physical examination by the physician, and screening mammography as appropriate for age and risk factors should be emphasized. A woman with a solitary or dominant mass or an area of asymmetric thickening should undergo mammography to evaluate the mass, to identify additional suspicious areas, and to provide a baseline for future examinations. Regardless of the results of the mammogram, the woman should have fine needle aspiration of the mass. If a solid mass is aspirated, cellular material should be sent for cytologic evaluation. If fluid is obtained at aspiration and the mass disappears, no further evaluation is necessary. If, however, fluid is obtained by aspiration but a palpable mass remains, the needle may have missed a solid mass next to the cyst or entered both a solid mass and a cyst, diluting the aspirated cells with benign cyst fluid. In this situation, the remaining solid mass should be immediately reaspirated and a specimen from the solid mass sent for a cytologic examination.

If the cytologic finding is of malignancy, the patient should be referred for a surgical evaluation. Suspicious cytologic findings should be followed by an excisional biopsy. Benign cytologic results in the setting of a mammogram

showing no features of malignancy require a careful clinical evaluation at six-month intervals. If the findings of a physical examination are suggestive of breast cancer, or the mammogram suggests possible malignancy, an excisional biopsy should be done despite benign cytologic findings on aspiration.

Risk of Breast Cancer

Most types of benign breast disease are not associated with an increased risk for the subsequent development of breast cancer (Table 1). There is a slightly increased risk for women with hyperplasia or papilloma (relative risk = 1.5) and a moderately increased risk for women with atypical hyperplasia (relative risk = 5). In about 8% of women with atypical hyperplasia, and in as many as 20% of such women who also have a family history of breast cancer, breast cancer develops within 15 years. All women with atypical hyperplasia should be followed with a yearly physical examination, a yearly mammogram, and FNA or biopsy of any suspicious lump.

An increased risk of subsequent breast cancer has only been established for certain pathologic categories of fibrocystic disease diagnosed after biopsy. There is no proof of increased risk in women with breast lumps who have not had a biopsy. Of all women who do have a breast biopsy, only 2% to 4% have atypical hyperplasia. The proportion of breast lumps that are atypical hyperplasia among women who have not had a biopsy is not known but may be lower than among women who do have a biopsy because women who undergo biopsy tend to have other risk factors for breast cancer. Thus, perhaps 1% to 2% of all women with lumpy breasts who have not had a biopsy are at increased risk for breast cancer. Unfortunately, these women cannot be distinguished from women not at increased risk by physical examination, mammography, or FNA cytologic examination. We do not feel that the increased risk in 1% to 2% of women with breast lumps justifies diagnostic mammography or tissue sampling in all such women.

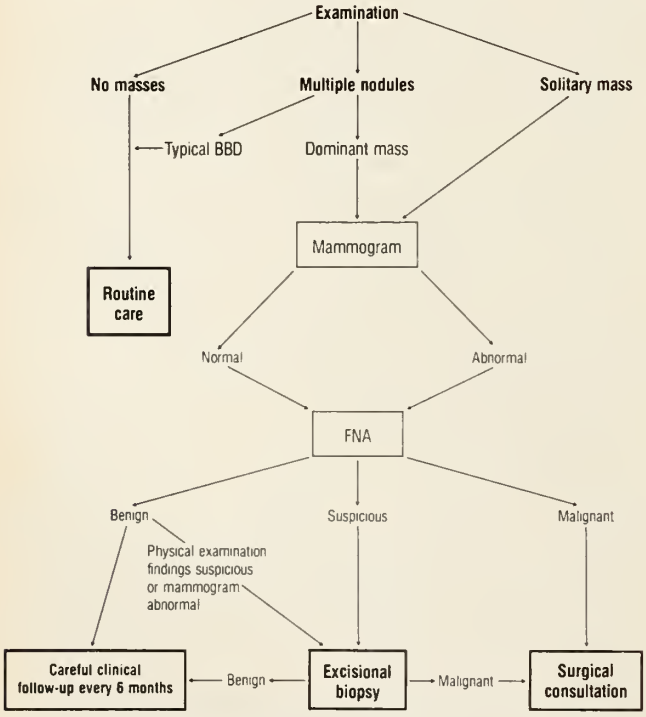

Figure 1.—The schematic shows the evaluation of a suspicious breast mass. BBD = benign breast disease, FNA = fine needle aspiration

TABLE 1.—*Pathologic Types of Benign Breast Disease Classified by Relative Risk for Breast Cancer*

Risk	*Type of Breast Disease*
No increased risk for breast cancer— 70% of all biopsies	Fibrocystic breast disease Adenosis Apocrine metaplasia Cyst(s) Duct ectasia Fibrosis Hyperplasia, mild Squamous metaplasia Fibroadenoma Mastitis
Slightly increased risk for breast cancer— 26% to 28% of all biopsies (relative risk=1.5-2)	Fibrocystic breast disease Hyperplasia, moderate or florid Papilloma
Moderately increased risk for breast cancer— 2% to 4% of all biopsies (relative risk=5)	Fibrocystic breast disease Atypical lobular hyperplasia Atypical ductal hyperplasia

Treatment

Many women with lumpy breasts have breast tenderness that intensifies during the last few days of the menstrual cycle, then resolves with the onset of the menses. The overwhelming majority need no treatment except the assurance that their discomfort is physiologic and not a sign of cancer. There is, however, a small group of women who have severe breast pain requiring symptomatic treatment. While a supportive brassiere may be somewhat helpful, many of these women need medical therapy. Also, there are a few women with benign breast nodules in whom dominant masses requiring aspiration or biopsy repeatedly develop. These women may desire treatment to reduce the need for such procedures.

Many medications have been advocated for the treatment of benign breast lumps. The two most publicized therapies—abstaining from methylxanthines (coffee, tea, chocolate, colas, theophylline) and taking low doses of oral vitamin E—are attractive because they are inexpensive and harmless. Studies of dietary abstinence from methylxanthines are conflicting, but there is some suggestion of efficacy. Two recent controlled trials showed no significant difference between treatment with vitamin E and placebo. Good results are anecdotally reported using moderate salt restriction, mild diuretics, and nonsteroidal anti-inflammatory drugs. Patients who do not respond to these simple modalities may respond to treatment with danazol. This medication has been shown in randomized controlled trials to be effective in relieving pain and nodularity, but it has substantial androgenic side effects that may not be reversible. Thus, danazol should be administered only by a physician familiar with its use.

Conclusions

Lumpy, tender breasts are common in women of all ages. Most of these women have no significantly increased risk of breast cancer, and therapy is necessary in only a small group of women with severe breast pain. The clinical task for pri-

mary care physicians is to distinguish benign breast lumps from breast cancer. Fine needle aspiration is a major advance in evaluating palpable nodules. Used together with physical examination and mammography, it can accurately distinguish benign from malignant breast masses.

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Circumventing Diarrhea

BISMUTH SUBSALICYLATE (PEPTO-BISMOL) is one of the agents now recommended to help control diarrhea; however, primarily in the young person but also in the older person who is on aspirin therapy for something like arthritis, salicylate intoxication may develop because there is salicylate absorption from this substance. Also, you need to warn patients about their stools becoming black. Many times, this is thought to be due to melena, but the bismuth will cause the stools to become black. Recently, one other thing has been thought to be true about Pepto-Bismol: bismuth salts are thought to be an antimicrobial agent that actually prevents multiplication of these organisms in the gastrointestinal tract. So, for these reasons, Pepto-Bismol is felt to be one of the mainstays now for control of acute diarrhea.

Kaopectate, which is an absorptive agent, is very safe. It works by making the stools more bulky. Remember, though, that the loss of fluid in the stools probably remains about the same, so patients are still at risk of becoming dehydrated, although they can control their stools a little better.

About 40% of patients from developed areas who go to a developing area are going to get travelers' diarrhea and about half of these are due to enterotoxigenic *E coli.*

You are probably also going to be asked about prevention of travelers' diarrhea. It is now thought that preventive treatment should be reserved for business people on critical short-term assignments or persons with significant underlying disease. The current recommendations are either to use trimethoprim-sulfamethoxazole or doxycycline as antibiotic agents to control and prevent travelers' diarrhea. Pepto-Bismol has also recently been shown to be effective, but you'd probably have to take another couple of suitcases loaded with Pepto-Bismol along with you in order for it to be useful. Probably it's most important that these travelers just carry trimethoprim-sulfamethoxazole or doxycycline with them and rapidly institute therapy if they do become ill, rather than trying to take it the entire time they are away. If they are going to be away for more than two weeks, it's inappropriate to use prophylaxis for travelers' diarrhea.

—FREDERICK W. DERKS, MD

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Seminars in Health Care Delivery

Evolving Principles of Office Quality Assurance

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The application of medical quality assurance principles to ambulatory patient care using the traditional methods of medical chart audit, process review, and physician education has yielded generally disappointing results in improving patient care and physician performance. Newer methods assist physicians by providing patient and medical reference data at the time of a patient's visit. Techniques for tracking treatment outcomes and patients' test results and for providing instructions to patients may improve both care and patients' and physicians' satisfaction.

This feature appears regularly in THE WESTERN JOURNAL OF MEDICINE. It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.

STEVEN A. SCHROEDER, MD
Series' Editor

Providing high quality patient care is increasingly becoming a challenge with the forces that are affecting our delivery systems: increased medical technology and information, changing payment systems that favor reducing health care spending, and increased expectations that we provide preventive health care services. The traditional method of using the medical chart audit, followed by physicians' feedback and education, has been generally unsuccessful in favorably altering a physician's performance and patient care quality in a lasting fashion.[1-7] Assuring quality of care goes beyond assessing a physician's knowledge. Performance has been shown to be suboptimal at times, despite an adequate level of knowledge.[8-10] Numerous studies show that physicians do not adhere to published guidelines[11-16] or to their own standards[17-20] in providing preventive health care. Providing quality health care requires, in addition to physician competence, good office organization and management and attention to the details of the health care system.

In contrast to the lack of success of the traditional medical chart audit, there have been numerous studies that document improved patient care and physicians' performance when other innovative office techniques are used. Systems using computer-generated[15,21-23] and nurse-initiated[14,24] reminders have been shown to improve physicians' performance of acute care and preventive medical care tasks. Other methods appear promising but currently lack evidence of improving care. These include computer-assisted diagnosis support tools, "fail-safe" test result tracking mechanisms, and the use of patient care outcome data. Quality assurance measures that are viewed by physicians as onerous and an imposition on their practice discourage physicians' participation and provide little incentive for use.[25] Understanding the strengths and weaknesses of traditional audit methods and comparing these with newer interactive techniques allow a physician to develop office systems that improve patient care and, quite likely, professional satisfaction.

Traditional Quality Assurance Techniques

The medical chart audit and site survey, followed by educating physicians and perhaps reassessing problems at a later date, compose the traditional method of assuring quality medical care. Three types of criteria are generally investigated: structural, process, and outcome. Structural criteria are those that are the easiest to measure. These judge the adequacy of such things as office equipment, facilities, services, personnel, staffing patterns, and credentials. The Joint Commission on Accreditation of Healthcare Organizations, for example, uses these criteria for approving hospitals, even to the point of counting defibrillators, measuring lighting in hallways, and reviewing financial patterns. Although important and easy to study, these do not necessarily improve patient care outcomes, which is a weakness of this type of review.[26,27]

Process criteria are those that describe what is actually done to or for a patient and how the physician uses knowledge and resources for patient care. This information is generally derived from medical records or patient interviews. This method scrutinizes the diagnostic tests chosen, medications used, appropriateness of laboratory and x-ray film follow-up, and the adequacy of documentation in a medical record, for example. Advantages of these criteria are that they rely on the medical record, which is generally available, the process is inexpensive, and nonphysician reviewers and predetermined objective criteria can be used. Disadvantages are that the review occurs retrospectively, at times long after the care was given; standards vary widely and are difficult to estab-

Norman LA: Evolving principles of office quality assurance. West J Med 1988 Aug; 149:230-233

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lish; medical record review depends on the accuracy and completeness of the medical record; and, finally, the outcome, favorable or not, may have little to do with the process that was used.

The goal of examining structure and process criteria has been to identify those variables that are consistently correlated to favorable patient care results. As noted above, few studies document the success of these measures.

Contrast these criteria to outcome measures, which examine patients' health status at the end of treatment. Measurable outcomes include satisfaction, comfort, disease resolve, the ability of self-care, improved mobility, and ability to return to work. The advantages of examining outcomes are that they are more objective, reliable, and relevant, with patients acting as their own controls. Outcomes theoretically depend on "adequate" structure and process variables, including patients' compliance, and address cost concerns. Examining outcomes theoretically is a method of comparing providers and focus attention on the recipient of care—the patient. Outcome may be independent of the treatment given, however, and patients' satisfaction may not be a good indicator of the quality of care. Treatment outcomes may be years away, as in many types of chronic diseases, and interval measures are probably more meaningful in these instances. In using outcomes to compare the quality of care given by different providers, one must cautiously interpret statistics that would penalize those who care for the sickest patients. Last, each patient has unique variables that make the comparing of outcomes difficult.

The assumption in examining structure, process, and outcome variables is that when deficiencies are found and physicians are educated about them, lasting performance changes will occur. This assumption has generally not been found to be valid.[1-10,26-28] Behavior often adjusts during or just after an audit period, but when reaudited a year later, performance is found to be unchanged from preaudit levels.

There are reasons for poor compliance with and disappointing results from these types of quality assurance interventions. Physicians often do not like to participate. Audits are viewed as tedious added work, annoying, and imposing on their practice. Depending on the comprehensiveness, they can be costly. Physicians have been shown to have poor insight into how they themselves actually practice, in comparison to what they see as their "ideal." Because physicians tend to think that their performance is better than it really is, their perceived need for quality assurance interventions is probably low. One study[28] showed that on certain important practice tasks to be done at at least a 90% compliance rate, the physician group who determined the ideal rate actually practiced at a compliance rate of 30% below their own ideal. Other studies[18-20] show that physicians' compliance with cancer screening procedures is far below their own standards for themselves.

Additional reasons for poor results with traditional methods are that many of the failings are due to systems problems out of a physician's control—lost laboratory slips and patients' noncompliance, for example. Many physicians and offices simply run out of enthusiasm by the end of an audit, and meaningful changes are not implemented.

It is because of these emerging data that quality assurance programs based primarily on the medical audit are being viewed with skepticism. Although a sincere attempt, such measures do not achieve quality assurance goals and do not help physicians to practice medicine. Patient outcome will remain an important quality assurance indicator. Targeted outcome measures that are particularly applicable to ambulatory care practices need to be developed. Such measures include sentinel diagnoses, frequency of admitting to hospital, or the use of particular services, for example. A model of targeted quality assurance has been created by a panel of physicians evaluating the care of the elderly.[29]

Newer Approaches

The assumption that guided traditional quality assurance programs in the past was that what was needed was the education of bad physicians, not reminders to good physicians about what they already know.[21,28] In reality, significant errors are seldom caused by insufficient medical knowledge. More commonly, errors are caused by such things as missing or faulty data, inadequate decision-making time, a lack of access to information in patients' charts, an inability to read chart entries, forgetting to follow preventive care guidelines, or simply letting important patient information or follow-up slip through the cracks. In recognizing these shortcomings—what McDonald calls the "non-perfectability of man"[21]—a new assumption is emerging that will probably guide future quality assurance efforts: Physicians will generally do the right things if they have the information with which to make decisions. If one does not think that this is true, then quality assurance programs will be destined to fail.

The thrust of newer efforts in quality assurance is to provide information to physicians that is helpful, relevant, legible, and available at the time of a patient's visit. Only recently have good computer-supported clinical information systems been designed for physicians' offices that can help to achieve these goals.[15,29-32] Some of the specific methods are discussed here.

Patient Data Base

A recent article by Chan and colleagues showed how one medium-sized practice used a standard computer and a software package to organize a patient data base.[33] The information was depicted on every patient contact form. The elements of the data base were demographic data, family genogram and social data, problem list and medical history, medications, allergies to drugs, health maintenance record, progress note, laboratory data flow sheet, and relevant patient correspondence. While many do not consider a good patient data base to be a quality assurance method per se, easily accessible information is a prerequisite to making good patient care decisions.

Physician Reminders and Logic Protocols

Various physician-authored systems have been developed to assist physicians in managing patients.[15,21,30-32,34-36] The systems have in common a goal of taking the information a physician gets from a patient and making suggestions for the patient's further evaluation and management. These reminders to the physician are triggered by the clinical condition identified, the laboratory and x-ray film data put into the system, and the knowledge of what is already in the patient's data base. The physician may or may not choose to act on the suggestions.

The Regenstrief Medical Record System, developed by McDonald,[34] is an example of this type of system. Physician-authored protocols generate feedback, such as,

- Reminders of possible drug interactions,
- Other possible diagnoses: "based on the clinical, lab[oratory], and x-ray data, consider these additional diagnoses . . .,"
- Medicine dosage adjustment recommendations,
- Preventive medical screening interval: "Pap smear due,"
- Laboratory follow-up recommendations: "based on the low [hematocrit] or [hemoglobin], check these additional reasons for anemia . . .,"
- Assurance of follow-up on therapy: "has β-blocker for angina worsened [chronic obstructive pulmonary disease]?"

Many new systems are being developed, and a wide selection of protocols are and will be available that will meet physicians' unique practice needs. Some of these clinical protocol systems can be added to administrative computing systems already in use in office practices.

Fail-Safe Mechanisms

Lost laboratory, x-ray film, or other diagnostic test results increase the likelihood of missed or delayed diagnoses. Physicians need tracking systems to notify them when tests are done or not done, that acknowledge that they saw the result and "signed it off," and that they made a determination based on the result. From a risk management perspective, lost data, or those tests that were hurriedly or incompletely dealt with, place physicians at an increased risk of malpractice. Computerized or manual office systems need to be developed to keep a tally of tests that have been ordered and are outstanding. As the physician receives the results of tests and "signs them off," they can be removed from the list. Although such a mechanism does not ensure that the follow-up on the test was appropriate, it is helpful to know that the test was done and the result acknowledged. This is preferable to relying on a patient to "call back in a few days for the result."

Generic Quality Assurance Screens

In any medical practice—particularly in large offices—it is difficult but important to track patients' outcomes. Generic quality assurance screens have been developed for hospital inpatients to be used as a part of a hospital's comprehensive quality assurance program, as in the Medical Management Analysis system developed by M. J. Craddick. These are not widely available for office practices, however. I am currently developing a system whereby physicians indicate, at the time of each patient's visit, an appropriate quality assurance outcome screening item. My list includes such items as no occurrence of quality assurance significance, office visit for an adverse outcome, an infectious complication, a medication error, and patient's dissatisfaction. The list can be brief and manageable. At the end of each month, or at whatever time interval chosen, the information can be displayed as individual physician or aggregate provider data. In effect, the process functions as an outcome screen on every patient's visit. Because it is completed at the time of a patient's visit, the data are not dependent on recall and take no additional time to record once the provider becomes familiar with the list. This may be an effective quality assurance and risk management tool, although it has not been prospectively tested.

Reference Systems

Computer retrieval systems are being developed for online reference material. For example, information such as that in the *Physicians' Desk Reference* can be made rapidly available, saving the time spent looking up the information in a book.[37] Likewise, using a telephone modem, articles can be retrieved from the National Library of Medicine.

Patient Instructions

On leaving a clinic, patients can be given instructions about their test results, illness, and medications. While this is currently being done manually in many practices, computer systems have been developed to generate these instructions.* Although they have not been tested prospectively, such instructions may improve compliance, patients' satisfaction, and perhaps quality of care.[38]

Summary

The newer approaches I have described suggest that office computerization is desirable. Because this shifting focus is based on providing a physician with information, it does lend itself well to the "gopher" work of fetching, organizing, reviewing, and recording[36] that computers do so well. Many of the principles, with some creativity at each physician's office, can be manually implemented, however. These methods will likely provide physicians with better access to the rapidly expanding body of medical information. It is hoped that by using proven quality assurance methods and information to support physicians' decision making, an integrated system will emerge that improves physicians' satisfaction and patients' outcomes.

*Two such systems are the Clinical Reference Systems, Inc, Englewood, Colo, and the Lynx Medical Systems, Inc, Bellevue, Wash.

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Seven Commandments of Medical Consultation

I HAVE COME UP WITH THE SEVEN COMMANDMENTS OF PREOPERATIVE EVALUATION, in terms of being a medical consultant. If you keep these in mind, I think you'll always do a good job and you'll also be able to teach your students or people who work for you how to do a good consultation.

Assessment must be *C*omplete. That includes looking at old records to find out what has transpired. The most common one is cardiograms that have changed in the last couple of years.

You must *O*versee the case for which you were consulted; don't stray into other areas that you weren't asked to see in that patient. You might be treading on territory that doesn't belong to you. That often happens at our place when hematology is involved, for instance. We're asked to see the patient for a specific pulmonary problem, and we start commenting about the hematologic problems.

Promptness is *N*ecessary; I think that's important.

*S*alient recommendations are called for; be precise. "Cleared for surgery" at the end of the consultation with no other recommendations is pretty shallow. "Cleared for surgery with no recommendations" might not stand up in court too well.

*U*tilize frequent communication. Please talk to the physician who has referred the patient to you.

Don't rely on *L*iterature to substantiate: the people who consult you don't care how much you can quote the literature on the latest therapy.

If there is something important, you can work it into your recommendations and make it a valuable *T*eaching process for your consultations.

If you put these all together, all seven items, they spell *CONSULT.* I think if we keep just these points in mind, we can then convey this to our younger people coming up and, of course, make some points with the people who consult us.

—GENO J. MERLI, MD

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Medicine in Perspective

Experience of a Clinic for Afghan Refugees in Pakistan

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Since the Soviets invaded Afghanistan in 1979, 3.5 to 4 million refugees have moved into Pakistan and Iran. Even before the war, the health status of the Afghans was extremely poor and the medical personnel limited. Various international efforts are attempting to cope with the health care needs of the refugees. Economic, language, and cultural problems hamper the projects. One clinic found the most common problems were of the gastrointestinal tract, then the respiratory tract, with a problem ranking similar to that of pre-war Afghanistan. Many of the health problems are linked to deficiencies in sanitation and nutrition.

(Morgan WA: Experience of a clinic for Afghan refugees in Pakistan. West J Med 1988 Aug; 149:234-238)

Afghanistan is a landlocked country with Russia along its northern border, Iran on its west and southwest, and Pakistan on its east and southeast borders. Most of the population centers are along the east, and the major trade routes have traditionally been from Pakistan across many mountain passes, including the Khyber.

The Soviet Union invaded Afghanistan in December 1979. Bombardment and shelling of villages by the Soviets continued at least until the "Geneva Accords" were signed April 14, 1988. Some Soviet troops have withdrawn, but not all are scheduled by the Accords to leave until late 1989. Meanwhile, the Soviet-backed Afghan army continues the battle against the freedom fighters, or *mujahidin.* Refugees have streamed out of Afghanistan. About 3.5 million of the original 17 million population are now in camps in Pakistan and possibly 1 million are in Iran. Other millions have left the countryside for the relative safety of Soviet-occupied cities, especially Kabul. The *mujahidin* operate throughout the country but bring their supplies via the trade routes primarily from Pakistan and some from Iran. The *mujahidin* operate with strong emotional support from and identification with the villagers remaining in Afghanistan and also receive what little food supply and shelter the villagers can offer. For this reason, the villages, particularly along the Pakistan borders, were the target of intense Soviet attack, and farmlands were burned.[1]

Even as the Soviets withdraw and some towns are won back by the *mujahidin,* the return of the refugees is being delayed by the danger of an estimated 3 to 5 million land mines left by the departing Soviets. The United Nations is planning a de-mining operation, which may take years, and thousands may die from undetected mines (J. C. Randal, "Soviets Leaving Deadly Farewell Gift for Afghans," *Sacramento Bee,* June 26, 1988).

Since 1979, the Russians have suffered an estimated 25,000 deaths, according to Soviet sources quoted by the US Department of State.[2] The death and destruction suffered by the Afghans have been extreme. Many of the Afghan victims are civilians, including women and children, and are victims not only of direct attack on their villages but also land mines and bombs disguised as toys and other innocent and attractive devices. The Afghans also suffer from diseases associated with poor nutrition, poor sanitation, environmental exposure that includes both intense dry heat in the desert regions in the summer and severe snow and winter storms in the mountains, and the emotional trauma caused by the destruction of their lands, by the death of family members, and by dislocation.[1]

Even before the invasion, the health status of the Afghans was critically poor. By 1979 census and survey data, the life expectancy at birth was about 41 years, probably the lowest in the world, with a crude death rate of 22 per 1,000 population. Infant mortality was 182 per 1,000 population. Births averaged up to 8.2 per married woman, among the highest ever recorded, with 81% surviving to age 5 in urban areas, 61% in rural areas. Maternal mortality may exceed 100 per 100,000 live births.[3] In 1973-1975 hospital clinic studies in Kabul, 92.6% of children were found to have intestinal parasites, most of them ascariasis, *Giardia,* and *Entamoeba histolytica,* in that order. Tuberculosis was found in 2% to 3% of the population.[4] Malnutrition was recorded in 67% of children admitted to hospital.[5] Gastroenteritis was the major cause of admission for these children, followed by respiratory tract infections. The case-fatality rate for all pediatric admissions for all diagnoses was 8% and that was in the major children's hospital in the country.[5]

Intensive epidemiologic studies of several rural Afghan villages in 1967-1968 disclosed an infant mortality rate of 205 per 1,000 live births, with 3.8% of adult women reporting at least one stillbirth.[6] Malaria was found in 20.8% of children in lower altitude villages, *Shigella* in as many as 7.1% of all children, *E histolytica* in 6.8% to 21%, and *Giardia* in 3% to 11.7% in the various villages studied. Of adult chest x-ray films, 3% showed tuberculosis, 1.2% being cavitary.[6]

The availability of health professionals in Afghanistan has never been good and has deteriorated substantially since 1979. Two medical schools had produced one physician per 11,000 population. These physicians were not well dispersed through the countryside but rather concentrated in more

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ABBREVIATIONS USED IN TEXT

IMC = International Medical Corps
USAID = United States Agency for International Development

urban areas.[4] Because the physicians traditionally came from more influential families and the medical schools had ties with western countries, they were in great danger from the invading Russians. Most of the Afghan physicians fled Afghanistan early after the invasion or were killed. Most who fled are now in Europe or India. Only a few remain in Afghanistan who are available to help the rural people and the *mujahidin*, and a few are in the refugee areas. Probably a dozen portable hospitals are available that move frequently with the tides of war. (Foreign medical personnel, especially European and American, have traveled with the *mujahidin* throughout Afghanistan, but this is discouraged by governments because of the danger. Some have been killed.) Nursing and other allied health professionals also were scant before the war and are further decimated now.

Health care for women has always been a particular problem because tradition argues against both the examination of women by male practitioners and higher education of women in professional roles. By the 1979 census, only 31% of women had any formal education at all, compared with 63% of men.[7] Few women had gone on to medical or nursing school, and fewer still are working in the area now. The education and status of women was one of the issues that divided the political parties, especially before the invasion.[8]

Medical evacuation is also a particularly hazardous enterprise for the *mujahidin* and the injured and sick civilian populations. There is no air evacuation, roads are few and under constant attack, and vehicles are functional for only short distances. Evacuation must be by camel, donkey, or horse and most commonly on foot. Most places in the country are many days, even weeks, of travel to safe medical care in Pakistan or Iran. The evacuation problem has greatly increased mortality and morbidity.[9]

Medical Care for the Refugees

Little is known in the West about medical care available to the Afghan refugees in Iran. In Pakistan, many organizations are involved in medical care, but even together they cannot meet the great need. Coordination of their services is attempted by the Pakistan Department of Health, particularly for clinics that operate directly within the refugee camps. The United Nations High Commissioner for Refugees, in conjunction with the World Health Organization and World Food Program, organizes relief efforts for the refugee camps. Their efforts have included safe drinking water through deep wells and the distribution of tents, blankets, and food stocks, particularly wheat, flour, soyabean oil, tea and sugar, and dried milk products for mothers and children. The adult food allotment is based on 2,200 calories per day, but distribution is erratic and incomplete.[10]

Primary care clinics have been established in many of the refugee camps, staffed mostly by Pakistani physicians and other health workers and organized by the high commissioner and the health department of the North-West Frontier province of Pakistan. Other refugee clinics are operated by relief efforts from European nations, Saudi Arabia, and the United States, using Afghan, Pakistani, and foreign personnel.

Numerous hospitals in the more urban areas of Pakistan along the Afghan border serve refugees from many camps and receive the wounded and sick directly as they come from Afghanistan. The Khyber Hospital, run by Pakistani physicians in Peshawar, is the largest. Another is an excellent hospital particularly for trauma patients operated by the International Committee of the Red Cross, administered by Swiss, and staffed mostly by western European physicians and staff. Saudi Arabia and Kuwait run hospitals for the Afghans both in Peshawar and in Quetta. Five of the seven principal political parties of the Afghan resistance run small 20- to 40-bed hospitals. They are ill-equipped but are run entirely by Afghan personnel. Also, there is the Afghan Surgical Hospital supported by a Pakistani Islamic charity and with visiting physicians from Orthopaedics Overseas, a US-based group. The Afghan Obstetrics-Gynecology Hospital has several Afghan women physicians and midwives and Pashto-speaking Pakistani women physicians, with US physicians visiting under the auspices of International Rescue Committee, Rotary International, and, recently, the American Aid for Afghans. An excellent eye hospital has been run by two generations of American missionary ophthalmologists, with US and European backing, since the 1960s. All of these hospitals are crowded. They serve urgent needs of the Peshawar and Quetta areas fairly well, but many less urgent problems cannot be dealt with. The needs of refugees farther from these cities are even less well met.

Language barriers complicate health care. Most Afghan refugees speak Farsi and many speak Pashto, a language that is native to tribes on both sides of the border. Several other languages are spoken by the Afghans. Some of the Pakistani health professionals speak Pashto, but most speak Urdu, a language not understood by the Afghans. The Saudi and western workers rarely speak Afghan languages.

Several programs train Afghan *mujahidin* to be paramedics. The French, Belgians, Germans, and Saudi Arabians run programs, as do three American groups: Mercy Corps International, Freedom Medicine, and the International Medical Corps. The western country projects are all private volunteer organizations, rather than government-operated, though most have some government subsidy. The US Agency for International Development (USAID) contributes to projects operated by many nations. Some of these programs focus their training only on battlefield trauma while others include primary care because of the illnesses suffered by the *mujahidin* and by the civilian population in Afghanistan. The students for these programs are commonly selected by *mujahidin* commanders, and after graduation they return to their fighting units. Training programs run 6 to 18 months. Some programs issue medical supplies for their graduates to take into Afghanistan with them, and some programs continue to supply them. A Swedish group also operates an extensive medical supply system.[9]

The USAID has contributed $480 million to many of these health, training, and food projects through fiscal 1986, including to European private volunteer organizations.[2]

The Nasir Bagh Clinic

In March 1986, a clinic was opened by the International Medical Corps (IMC) adjacent to a large refugee camp of about 32,500 Afghans. The Nasir Bagh area is eight miles southwest of Peshawar, located in the rocky flatlands at the base of the mountains along the Afghan border. The clinic is

a concrete and brick structure initially having ten rooms, including a separate entrance and waiting room and two examination rooms for women and a waiting room and four examination cubicles for men. The clinic has electricity most of the time, a septic tank, and deep well water. The facility has subsequently been enlarged.

The clinic was established in part to serve as a training clinic for the paramedics being trained by the IMC. The opening of the clinic coincided with the clinical phase of the first class of 45 students. These students rejoined their regiments in the summer to be replaced by subsequent classes. Medical personnel for the clinic included initially two Afghan physicians and volunteers from the United States, including a succession of short-term physicians, nurse practitioners, physician assistants, nurses, and medical students, who served with the help of translators. Afghan paramedic students examined the patients and presented to the physician staff, who reexamined and helped with the diagnosis and management.

The clinical laboratory initially consisted only of a microscope for malaria smears, but subsequently had the capacity for measuring hemoglobins and doing blood counts, urinalyses, stool examinations, sputum smears, pregnancy testing, and blood typing. That diagnostic facility was not available during the first several months of the clinic's operation. Radiology was not available in the clinic, but x-ray films could be obtained by referring patients to hospitals in Peshawar, usually at great cost to the patients. Simple radiology has recently been added to the Nashir Bagh Clinic. The clinic pharmacy dispensed medication purchased by the IMC or donated by benefactors in the US. This resource was generally satisfactory. Referral for hospital admission was to selected hospitals in Peshawar as described above. The teaching and clinic operations continue as of this writing.

Diagnoses and Medical Problems

A one-page medical record is written for every patient on every visit, filed both by date of visit and by sequential number. The record is written in a subjective-objective-assessment-plan format, with the patient's name and estimated age included. The clinic began seeing patients on March 22, 1986. For the first 50 working days thereafter (through June 4) the clinic registered 2,409 patients, averaging 48 patients a day. Half of these were on the "women's side" and half on the men's, although the patients seen on the women's side were mostly children the women brought. Overall, 47% of all registered patients were pediatric

TABLE 1.—*Age and Sex Distribution of Afghan Refugee Patients Seen in Nasir Bagh Clinic, Pakistan, April 16 to June 2, 1986*

Age	Sex: Female, No.	Sex: Male, No.	Total: No.	Total: %*	
0-11 mo	60	97	157	13	
12-35 mo	46	63	109	9	
3-13 yr	140	169	309	25	
Pediatric total	246	329	575		47%
(% of pediatric patients)	(43)	(57)	(100)		
14-44	149	252	401	33	
45-59	51	67	118	10	
60+	38	81	119	10	
Adult total	238	400	638		53%
(% of adult patients)	(37)	(63)	(100)		
Clinic Total	484	729	1,213		100%

*Percent of all patients.

TABLE 2.—*1,232 Clinical Diagnoses in 1,213 Afghan Refugee Patient Visits to Nasir Bagh Clinic, Pakistan, April 16 to June 2, 1986*

Diagnosis or Complaint	Total	Per 1,000 Clinical Diagnoses*	
General Symptoms	134	109	(11%)
Fatigue/weakness	10	8	
Malnourished	21	17	
Anemia	14	11	
Headache	13	11	
Anxious	23	18	
Depressed	5	4	
Fever	28	23	
Malaria	20	18	
Skin Problems	89	72	(7%)
Impetigo	13	11	
Fungus	18	15	
Scabies, pediculosis	9	8	
Eczema	11	9	
Other (insect bites, milia, minor laceration, burns, abscess)	38	31	
Eye	26	21	(2%)
Conjunctivitis, stye, blepharitis	26		
Ears, Nose, and Throat	181	147	(15%)
Otitis media	42	34	
Upper respiratory tract infection	59	48	
Pharyngitis/tonsillitis	58	47	
Other ear, nose, and throat problems (otitis externa, wax, thrush, stomatitis, mumps)	22	18	
Pulmonary	150	122	(12%)
Bronchitis, pneumonia	113	92	
Asthma, emphysema	19	15	
Possible tuberculosis	18	15	
Cardiovascular	32	26	(3%)
Congestive heart failure	10	8	
Chest pain	5	4	
Miscellaneous cardiovascular problems (blood pressure abnormalities, palpitation, rheumatic heart disease, congestive heart disease, venous thrombosis)	17	15	
Gastrointestinal	359	291	(29%)
Indigestion, hyperacidity, peptic ulcer	48	39	
Vomiting and diarrhea	25	20	
Diarrhea	167	136	
Abdominal pain	27	22	
Constipation	15	12	
Parasites, ascariasis	67	54	
Rectal problems	10	8	
Musculoskeletal	143	116	(12%)
Arthritis, arthralgia	39	32	
Back pain	28	22	
Musculoskeletal trauma	24	20	
"Aches and pains"	52	42	
Genitourinary (urinary tract infection, prostatitis, miscellaneous)	40	32	(3%)
Gynecologic	9	7	(1%)
Healthy	50	41	(4%)
Other Miscellaneous	19	15	(1%)
Total	1,232	1,003	(100%)

*Numbers will not always add up to total due to rounding of fractions.

(younger than 13 years by estimate). For age, sex, and diagnostic analysis, medical records of 1,213 consecutive visits between April 16 and June 2, 1986, were tabulated (Table 1).

Table 2 lists 1,232 diagnoses recorded for the 1,213 visits. Given the lack of laboratory and radiologic confirmation, diagnosis was made almost exclusively on clinical grounds. The most common reason for presenting to the clinic was gastrointestinal problems, which made up 30% of the total. Half of these were for diarrhea and most of the remainder for epigastric distress of a more chronic nature resembling gastritis or peptic ulcer disease. Of the cases of diarrhea, most of the acute problems were in infants younger than 3 years. The gastritis symptoms are much more prevalent in the age group estimated between 14 and 44 years.

The second largest diagnostic grouping was ear, nose, and throat problems, making up 15% of the total. Most of these patients were children. Pulmonary problems ranked third at 12%, most of which were bronchitis. These were scattered in all age groups. Musculoskeletal problems was the fourth category and involved mostly chronic minor aches and pains. Miscellaneous generalized symptoms such as weakness, emotional problems, and malnourished infants made up 11% of the total visits. Skin problems composed 7% and were found mostly among children. Genitourinary, cardiovascular, eye, and gynecologic problems followed in that order, each accounting for less than 4% of all visits. In all, 4% were considered healthy without any significant diagnosis. There were 20 cases of malaria, most of which were confirmed by microscopic examination of a blood specimen.

Infant malnutrition seemed prevalent. A great many infants seemed thin and weak and were generally well below normal on growth charts. Anthropometric data were not collected, however, and marasmus, though seen, was not rampant. The cause of malnutrition apparently lies mostly in infant feeding practices rather than food shortage. It is traditional to breast-feed infants until they can take table food, commonly from 9 to 12 months of age. Infant cereals are seldom used. During the breast-feeding period, a mother's milk production is often low due to her own marginal nutritional status. Malnourished infants are of course susceptible to infectious diseases. It is not known whether infant death rates in the refugee camps are different from the high Afghanistan rate discussed earlier.

Discussion

In the Nasir Bagh Clinic, as elsewhere, many social and religious issues affect the way medical care is organized and provided, and even the way data can be gathered and reported.

Status of Women

Of the adults seen in the clinic, 63% were men and 37% were women. This number of women was higher than experienced by many clinics and may have been a reflection of the initial availability of women nurse practitioners. American women physicians, nurse practitioners, and physician assistants continue to serve this clinic. The existence of male professionals and students in the clinic discouraged women from attending, or, more accurately, signaled the men in the community to discourage or deny the women access to the clinic. On at least two occasions, an older man entered the waiting area outside the clinic and shouted that it was improper for women to be seen there and that they should go away. They all did. Many returned two or three hours later.

Women commonly would bring children to the clinic, which often seemed an access route for the women to get care for themselves. When they felt they were in a safe environment, they allowed a physical examination of chest, heart, and abdomen, but no pelvic examinations were done in the first four months of the clinic. Gynecologic problems were referred to the Afghan Obstetrics-Gynecology Hospital, although many women would not or could not accept that referral, nor could that hospital care for the great demand. During a hiatus of almost two months when there was no woman provider available, women patients continued to come to the clinic to be seen and examined by American male physicians. Again, it may be that the children served as a legitimate access to this care.

Of children brought to the clinic, 57% were boys and 43% were girls (Table 1); 70% were brought in by their mothers or other women. Of these, slightly more than half (55%) were girls. Fathers or other male family members brought in the other 30% of the children, 100% of whom were boys in a small sample of 70 children. (It was not uncommon for children to be brought to the clinic solely by older siblings who were themselves preteen-aged.)

Age

Birth dates and ages are not important in the Afghan society. No one knows their birth date, and most do not know the year and have only a rough idea of how old they are. It simply is not important to them. Reporting of data by age (Table 1) is based on estimates and therefore grouped in large age ranges.

Names

Afghan names tend to be one or two words for male Afghans, and one word for female Afghans. Because many names are common, Afghans are often identified as "son of . . ." or "daughter of . . . ." Again, a medical record system is made more difficult by the name similarity and by having no birth date as a backup identifier. There also is no number system such as social security numbers, nor is there any address other than the refugee camp name. Sometimes identification is augmented by the home province in Afghanistan from which a person came.

Language

As discussed, a refugee patient may speak one or two of many languages. On occasion, an Afghan doctor or student would have to translate one language into Farsi for the other Afghan providers, then a translator would translate to English for American providers.

Education

Few people can read or write. Formal education is and has been low. An understanding of health, disease, sanitation, and self-care is generally limited to traditions and myths. Health education in the clinic often begins not from a lack of information, but from misinformation, and must be verbal.

Poverty

Most patients have almost no money. Those who live in refugee camps receive food subsistence, which they may supplement by vegetable gardening and the husbandry of

sheep when space and grass allow. A few craftspeople and shopkeepers operate either in the refugee camps or in the main commercial areas of Peshawar. Most of these men left Afghanistan with both these skills and some capital. Those with more financial well-being have moved away from Peshawar, especially into Islamabad, Pakistan, or to India, Europe, or America. The poverty of those in the refugee camps is a major deterrent to health care in most cases. Although the refugees receive free attention and medication at the IMC clinic, they are unable to afford diagnostic studies that IMC does not do. The IMC clinic had more available free medication than most other clinics. Poverty does not seem to cause severe malnutrition directly, however. Apparently food distribution systems are adequate to prevent overt starvation.

Religion

The strongly Muslim people did not seem to have major health beliefs that negated medical care, except that during the holy month of fasting, many patients would not take medicine from before dawn until dusk.

Summary

In the first few months of operation of the Nasir Bagh Clinic by the International Medical Corps, a variety of primary care medical problems were seen. The diagnoses in the children seen were not unlike the distribution of causes for admission to the major pediatric hospital in Kabul reported between 1973 and 1975.[5] Problems at the Nasir Bagh Clinic will continue to be tabulated to identify trends and needs more closely, especially as better testing improves the accuracy of diagnosis. Also, comparison with other clinics will be sought. Although more precise epidemiologic survey data would be helpful for comparison and for assessing current needs, health needs are clearly great at both the preventive and the curative levels. The large proportion of gastrointestinal problems suggests sanitation to be a major problem. Marginal nutrition may underlie many problems, especially in the children. This needs to be better studied and addressed.

As the 3 to 4 million refugees begin repatriating to their homeland over the next few years, they will find little sanitation, few functioning schools, disrupted food supplies, and almost no medical care. Afghanistan will need sustained outside help to educate large numbers of health professionals, especially women, to establish and support a health care system, to develop a safe water supply and adequate food supplies with even distribution and safe storage, to develop sewage and sanitation systems, and to provide mass public education in health matters.

In the meantime, the concerted efforts of the United Nations, the World Health Organization, the World Food Program, the Pakistan government, and the efforts of a host of international organizations and individuals will continue to be needed to meet the health needs of the refugees. Pakistan receives the brunt of refugee problems second only to the refugees themselves. It has done so with patience and grace, largely because of Islamic brotherhood. But Pakistan itself is a poor nation, with a marginal economy and with limited land. International response, though critically helpful, has been less than it could be, due in part to relatively scanty news media coverage of the situation, that in turn is due to geographic and social distance. The problems are real and deserve international attention.

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Lessons From the Practice

Faye—An Unforgettable Patient

WILLIAM B. GALLAGHER, MD, *Tucson*

A 22-year-old woman in the second trimester of her second pregnancy developed severe diarrhea and was admitted to hospital. She was having 18 to 20 bloody, loose mucoid stools daily with abdominal cramps. Although treated with diphenoxylate with atropine, tincture of opium, and intravenous fluids, she continued to worsen, losing appetite and weight.

After three months, she was transferred to another hospital about 50 miles from her hometown. When admitted she appeared pregnant, emaciated, and dehydrated; her abdomen was diffusely tender, and fetal movements were detectable.

A subclavian line was placed, and parenteral nutrition and medications were begun. Proctoscopy showed bloody, inflamed, ulcerating rectal mucosa. Her abdomen became more distended and tender; abdominal films showed free air.

Her internist had been worried from the start. He kept hounding the obstetricians and surgeons to share his concern and to look at the patient frequently. His concern was justified. An operative procedure showed that her transverse colon was inflamed, necrotic, and spontaneously perforated in four places. Feces lay everywhere and the peritoneum was fiery red.

The surgeon transected the terminal ileum just proximal to the ileocecal valve, mobilized the colon transecting the lower sigmoid, and after removing the bulk of the severely-diseased colon, fashioned a right lower quadrant ileostomy and a left lower quadrant distal-sigmoid mucous fistula. The mucosa of the retained sigmoid was swollen, friable, and ulcerated. The excised colon showed acute colitis, necrosis, ulceration, microabscesses, pseudopolyposis, and perforations.

The next day the patient went into labor, which was rapid and precipitous, and was delivered of a two-pound boy. Her sigmoid mucous fistula, apparently loosened during her uterine and abdominal contractions, sank out of sight. Her abdominal wall broke down in two spots below her abdominal incision, and small bowel content poured out. Her ileostomy did not function.

The baby lived for only 14 days in the neonatal intensive care unit.

The surgeon hoped the fistulas would close spontaneously; they did not. Weeks passed into months, and the surgeons and internist were at loggerheads. They agreed on supportive management and hyperalimentation, but the internist urged reoperation.

The surgeon was loath to reoperate and would write, "Patient not yet in shape for surgery," or, if fistula drainage momentarily diminished, he would write, "Fistulas appear to be closing."

Sinograms showed the fistulas to be from the distal ileum, confirming the obvious. Repeat proctoscopy showed the defunctionalized rectum to be ulcerated, inflamed, and stenosed.

In November of that year, two teams operated through the lower abdomen and perineum, removing the colorectal segment, lysing numerous adhesions, and closing four ileal fistulas. At this point the terminal six inches of ileum just below the ileostomy turned black. This segment was excised and a fresh ileostomy fashioned. The patient did well for a few days, then fistulous drainage recurred to the left of the ileostomy.

Thanksgiving had passed; now Christmas was approaching. In the hospital five months, the patient was emaciated and barely alive; her abdominal wall was bathed in small bowel content, sore, and excoriated. She developed decubitus ulcers on her back. She was irritable, sometimes irrational, and unable or unwilling to care for herself.

Her first subclavian line stayed in 19 days, the second, 26 days, the third fell out in 9 days, the fourth was still going well into its second month.

The relationship between the internist and surgeon was strained. They tended to avoid each other in the hall. The internist was always viewing things with alarm, and he was usually right. The surgeon tended to be optimistic, but what supported this attitude was seldom readily apparent. Sometimes they snarled at each other. The internist thought of everything; the surgeon thought he was doing all the work.

Charge nurses, team leaders, dieticians, health planners all offered what they could.

In December the patient took an ominous turn. She became confused, then obtunded. Her blood urea nitrogen level, previously normal, rose from 8 to 59 to 111 mg per dl.

In a desire to get protein-building amino acids and calorie-containing glucose into her, all the fluids she was getting were hypertonic and contained nitrogen. She was not receiving enough plain water to dilute the hyperosmolar intake. A medical student figured this out and explained it to the surgeon and internist. Her condition improved when some of the hypertonic fluid was replaced with 5% glucose in water and plain water through her gastrostomy.

One night she had a convulsive seizure. Spinal tap results showed sugar—39 mg per dl. Regular insulin had been ordered for her total parenteral nutrition solutions, and the nurses had also been placing it in her isotonic fluid.

More time passed. The internist wanted the surgeon to operate again or find someone who would. The surgeon was waiting for her fistulas to close. Her doctors could seldom agree on day-to-day clinical impressions.

(Gallagher WB: Faye—An unforgettable patient. West J Med 1988 Aug; 149:239-240)

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Faye—that was her name—was from Iowa farm country and of Irish descent, with red hair. She was losing her hair but somehow held on to her sense of humor, on her better days. Once her surgeon came into her room and found her talking on the telephone. When he asked who she was talking to, she replied, "I'm calling the other hospital" (the cross-town rival) "to get me the hell out of here!" She was just kidding.

One night in January her visiting husband had to stay all night because of a blizzard. Her doctors told her that this was a Catholic hospital, and the nuns would not tolerate any hanky-panky. Her husband, Les, also a redhead, blushed the color of his hair.

Late in January Faye became jaundiced. Her appetite, never good, disappeared. Her surgeon had found another contraindication to reoperation. Toxic hepatitis? A? B? Non-A, non-B? The jaundice cleared up.

Winter gave way to spring. In March her surgeon reoperated through a new incision, wending vertically between her ileostomy and her fistulas. A loop of small bowel was found kinked in the pelvis, draining to the outside through a small hole. Distally, the ileum was twisted and obstructed by adhesions. The operating team closed the hole, cut the adhesions, and untwisted the ileum.

Hope flared up. Faye's ileostomy started functioning, and fistula drainage ceased. But her latest incision started to pull apart—to dehisce. Her ileostomy drained steadily into the nearby fresh laparotomy wound. No bag could be fitted to the ileostomy.

With hope dashed again, Faye would not look at or help care for her ileostomy. She did not want to get out of bed, despite exhortations from nurses and doctors. She would scarcely talk to her husband, son, or parents when they came to visit. Her doctors were at their wits' ends.

Somewhere in here, no one later knew when, the Hinge of Fate turned. Faye's open operative wound was being bathed and dressed. The wound began to granulate and shrink in on itself. She began eating, making the gastrostomy feedings no longer necessary. She started looking out the window at the trees in full leaf. She started reading, watching television, talking, knitting, and quickly became an expert at caring for her ileostomy and the now rapidly healing wound. She gained weight, joked, walked in the hall, and even went outside. She turned into a beautiful young woman, a gorgeous redhead.

Her 5th subclavian catheter was removed after 101 days on line.

On the 341st hospital day, her husband and now 3-year-old son came to take her home. Nurses, aides, dieticians, cleaning ladies, nuns (who had been praying for her), and doctors said goodbye. The internist and surgeon—and their wives, who had shared the ordeal—celebrated.

Years passed. Faye helped and taught other ileostomy patients. Son Adam was 8 years old when she again became pregnant. She went uneventfully to term and delivered a fine, healthy girl. Two years later, she had another baby, a boy.

In addition to their three children, Faye and Les have cared for 16 foster children over the years. Adam is in his last year of high school, with excellent grades, and is headed for the university.

Faye is an unforgettable patient.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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NEAR STANFORD. Six Internists, all subspecialty trained and members of clinical faculty at Stanford, interested in an Associate with subspecialty interest and training. Should be well grounded in Internal Medicine. Send CV to Dr Bigler, El Camino Internal Medical Group, 125 South Dr, Mountain View, CA 94040.

CRESCENT CITY, CALIFORNIA. Exciting position available at a growing 24,000 visit ER in a rural, coastal community. Fee-for-service with possibility of six figure income. Send CV to Art B. Wong, MD, FACEP, EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

CALIFORNIA, SONORA. Staff Physician position available in 11-12,000 visit ER in quaint, historic, growing gold country community with fantastic recreational opportunities, one hour from Yosemite. Excellent opportunity in an academic and democratic group. Send CV to Art B. Wong, MD, FACEP, EPMG, 120 Montgomery St, Ste 1825, San Francisco, CA 94104.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, Administrator, 1400 E. Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

SOUTH CENTRAL WYOMING. Immediate practice opportunity for BC/BE Urologist. Well-equipped JCAH hospital for a service area of approximately 20,000 population. No state or city income tax. Relocation incentives. Superior hunting, fishing, camping, snowmobiling. Three hours to Colorado ski area, five hours to Jackson Hole. One and one-half hours to the mountains. If interested, please send CV and references to D. Abels, DO, Chairman, Recruiting Committee or Richard Mills, Executive Director, Memorial Hospital of Carbon County, Rawlins, WY 82301; (307) 324-2221.

PHYSICIANS WANTED. We have full and part-time locum tenens opportunities available with guaranteed incomes and paid malpractice. For more information, contact John Smith, Locum Tenens, Inc (A Division of Jackson and Coker), 400 Perimeter Center Terrace, Ste 760 WJM, Atlanta, GA 30346; 1 (800) 544-1987.

PHYSICIANS WANTED

DERMATOLOGIST. Visalia Medical Clinic has an opening for a BC/BE Dermatologist now staffed by one physician who has been with the Clinic for 15 years. Located in the San Joaquin Valley in central California and population approximately 350,000. Progressive city of 62,000, near national parks and the ocean. Compensation is incentive oriented with advancement to full partnership after one year. Excellent fringe benefits. If interested, CV to John G. Heinsohn, Administrator, 5400 W. Hillsdale, Visalia, CA 93291; (209) 733-5222.

FAMILY PRACTICE/GENERAL PRACTICE wanted for full-time practice to work three days a week and share with another Practitioner. Rural setting, good pay, nice people. Can commute for two nights a week, one hour Sacramento, one hour and 15 minutes Nevada City, two hours San Francisco. Contact Charles Rath, MD, 199 E. Webster St, Colusa, CA 95932; (916) 458-7739.

OPENINGS for one or two General and one Vascular Surgeon in 175 physician, multispecialty group. Offices adjacent to modern 230-bed hospital in suburbs of south San Jose near excellent recreational facilities. Competitive salary, generous fringe benefits including paid educational leave, vacation, insurance, and retirement. Contact Latimer H. Booth, MD, Chief, Department of Surgery, The Permanente Medical Group, Inc, 260 International Cir, San Jose, CA 95119.

GENERAL INTERNIST needed for large hospital-based multispecialty clinic. University associated residency program. Attractive salary and complete benefit package. Pleasant setting. BC/BE. California license required. Contact Dennis L. Ostrem, MD, Chief Internal Medicine, The Permanente Medical Group, Inc, PO Box 254999, Sacramento, CA 95865-4999 or call (916) 973-5781. An Equal Opportunity Employer.

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to:
Western States Physician Services,
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Or call (209) 252-3047.

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PHYSICIAN OPENING. Ambulatory care/minor emergency center. Full/part-time for Family Practice/Internal Medicine/Emergency Medicine trained, experienced physician located in Tacoma area. Flexible scheduling, pleasant setting, quality medicine. Contact David R. Kennel, MD, 5900 100th St Southwest, Ste 31, Tacoma, WA 98499; (206) 584-3023 or 582-2542.

ARIZONA-BASED PHYSICIAN recruiting firm has opportunities coast-to-coast. "Quality Physicians for Quality Clients since 1972." Call (602) 990-8080; or send CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

PORTLAND, OREGON. Established, rapidly growing practice seeks BE/BC Internist. Multispecialty group active in private and HMO practice with satellite office. Salary and benefits first two years lead to partnership. Send CV to SMC, 10535 NE Glisan St, Portland, OR 97220, Attn: Dick Hamilton; (503) 256-0594.

FAMILY PRACTICE, PUGET SOUND. 23 physician multispecialty group is seeking Family Practitioner. Our facility has in-house lab and x-ray facilities and is conveniently located one block from Level III hospital. Attractive salary and benefits; partnership opportunity. Send CV to Carol Larsen, Acting Director, c/o The Western Clinic, PO Box 5467, Tacoma, WA 98405.

RHEUMATOLOGIST. Immediate opening for BC/BE Rheumatologist with large prepaid group practice in San Francisco bay area. Busy clinical practice with opportunities for teaching and research. University appointment possible. Competitive salary. Generous benefit package. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, Permanente Medical Group, 260 International Cir, San Jose, CA 95119, or phone (408) 972-6560.

(Continued on Page 245)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 161)

October 1—**Breastfeeding in the 21st Century: Concepts, Controversies and Advanced Practice.** Albuquerque. Ramada Hotel Classic. Contact: Lact-Natch Breastfeeding Clinic, 3620 Wyoming NE, #102, Albuquerque 87111. (505) 298-6243.

October 6-8—**Management of Radiation Accidents.** Sheraton Old Town Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 7-8—**4th Annual Balloon Fiesta Lung Conference.** Fri-Sat. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

October 18-21—**Epidemiologic & Methodologic Problems in Determining Nutritional Status of Older Persons.** Sheraton Old Town Hotel, Albuquerque. Tues-Fri. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 28-29—**New Mexico Medical Society Interim Meeting** and **Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Journal Center Pyramid Holiday Inn, Albuquerque. Fri-Sat. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 11-13—**Adolescent Medicine.** Hilton Inn, Las Cruces. Fri-Sun. Contact:Marilyn Stark, NM Chapter, American Academy of Pediatrics, 7605 Mountain NE, Albuquerque 87110. (505) 265-7431.

December 1-3—**American College of Physicians—New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

December 9-10—**Trauma Update '88.** Clarion Four Seasons Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

February 24-26—**17th Annual New Mexico Thoracic Society Lung Disease Conference.** Taos. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 217 Truman NE, Albuquerque 87108. (505) 265-0732.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

August 13-15—**Retrieved Implants and Biomaterials** (Sponsor: UUMC). Snowbird, Cliff Lodge. Fri-Sun. Contact: Rosalie Lammle, (801) 581-8664.

September 22-24—**Central Association of Obstetricians & Gynecologists** (Sponsor: UUMC). Thurs-Sat. 10.5 hrs. Salt Lake City Marriott. Contact: (801) 333-0988.

(Continued on Page 244)

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INDICATIONS AND USAGE: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated

CONTRAINDICATIONS: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage or perforation.

K-DUR tablets contain micro-crystalloids which disperse upon disintegration of the tablet. These micro-crystalloids are formulated to provide a controlled release of potassium chloride. The dispersibility of the micro-crystalloids and the controlled release of ions from them are intended to minimize the possibility of a high local concentration near the gastrointestinal mucosa and the ability of the KCl to cause stenosis or ulceration. Other means of accomplishing this (e.g., incorporation of potassium chloride into a wax matrix) have reduced the frequency of such lesions to less than one per 100,000 patient years (compared to 40-50 per 100,000 patient years with enteric-coated potassium chloride) but have not eliminated them. The frequency of GI lesions with K-DUR tablets is, at present, unknown. K-DUR tablets should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

PRECAUTIONS: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Laboratory Tests: Regular serum potassium determinations are recommended. In addition, during the treatment of potassium depletion, careful attention should be paid to acid-base balance, other serum electrolyte levels, the electrocardiogram, and the clinical status of the patient, particularly in the presence of cardiac disease, renal disease, or acidosis.

Drug Interactions: Potassium-sparing diuretics: see **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies in animals have not been performed.

Pregnancy Category C: Animal reproduction studies have not been conducted with K-DUR. It is also not known whether K-DUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. K-DUR should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The normal potassium ion content of human milk is about 13 mEq per liter. Since oral potassium becomes part of the body potassium pool, so long as body potassium is not excessive, the contribution of potassium chloride supplementation should have little or no effect on the level in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: One of the most severe adverse effects is hyperkalemia (see **CONTRAINDICATIONS, WARNINGS,** and **OVERDOSAGE**). There have also been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration, and perforation (see **CONTRAINDICATIONS** and **WARNINGS**); other factors known to be associated with such conditions were present in many of these patients.

The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by taking the dose with meals or reducing the dose.

Skin rash has been reported rarely.

OVERDOSAGE: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see **CONTRAINDICATIONS** and **WARNINGS**). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-waves, depression of S-T segment, and prolongation of the QT-interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 243)

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH: St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

August 29—**NW Regional Perinatal Conference: Current Issues in OB/GYN, Neonatology and Pediatrics.** Coeur d'Alene, Idaho. Thurs. Contact: (509) 624-3182.

August 31-September 3—**Second International Forum of Otorhinolaryngology.** Seattle. Wed-Sat. Contact: U/W, Maria Lilja, (206) 543-1050.

September 9—**Update on Anxiety and Depression.** Seattle. Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

September 12-16—**16th Annual Family Practice Review Course.** Seattle. Mon-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

September 17-24—**Effective Management of Common Sports Injuries.** San Juan Islands. Sat-Sat. Contact: Kathy Rairigh, EPIC Expeditions, (208) 788-4995.

September 19-20—**Focus: Critical Care 1988.** Tacoma. Mon-Tues. Contact: Tacoma General Hospital. (206) 594-1268.

September 22-23—**Non-Ionizing Radiation.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

September 22-24—**Orthopedic Biomechanics.** Seattle. Thurs-Sat. Contact: VMMC.

October 12—**Management of Chemical Hazards.** Seattle. Mon. Contact: U/W, (206) 543-1069.

October 27-28—**Annual Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

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Portland, OR 97220-4199

6275 Lehman Dr.
Colorado Springs, CO 80918

(Continued from Page 241)

PHYSICIANS WANTED

WASHINGTON. Expanding physician-owned emergency group has opening for full-time career-oriented Emergency Physicians in south central Washington. Flexible work schedules, excellent working and living conditions. Send CV to EMP, PC, PO Box 805, Cheyenne, WY 82003; or contact Donald Kougl, MD, (307) 632-1436.

WASHINGTON. Openings for career oriented Emergency Physicians, BC/BE in Emergency or Primary medical specialty. In a Seattle metropolitan hospital with 35,000 annual visits. Excellent salary with partnership potential in stable, growing group. Contact Beth Welsh at Valley Medical Center, 400 S. 43rd St, Renton, WA 98055.

SACRAMENTO. BC/BE Family Physicians needed for full-time primary care clinic, part-time ER/part-time primary care clinic, or full-time in our ER. We are a large-staff model HMO offering competitive salary, excellent benefit package, and shareholder status. California license required. Contact Richard Fury, MD, 1001 Riverside Ave, Roseville, CA 95678 or call (916) 784-4620. EOE.

ASSOCIATE MEDICAL DIRECTOR. Excellent opportunity for BC physicians to become a part of the Medical Department of one of the largest utilization and case management corporations in the U.S. The company specializes in remote utilization review, and in managed medical care for corporate and insurance carrier clients coast-to-coast. There will be an opportunity to work with physicians and develop treatment plans and alternate treatment sites for patients on a nationwide basis. Opportunities for input into corporate programs and strategic planning also exist. Utilization review experience is preferred but not necessary. Specialty Board certification is required. Respond to Director, Medical Department, 3200 S. Highland Ave, Downers Grove, IL 60515-1223.

SAN FRANCISCO. Outstanding opportunity for BC/BE Internist, Family Practitioner, OB/GYN, or Orthopedic Surgeon at 260-bed community hospital in the dynamic South of Market area. Excellent opportunity to join busy, growing practices. Competitive salary and benefits package. Send CV to Walter Kopp, St. Luke's Hospital, 3555 Army St, San Francisco, CA 94110; (415) 641-6543.

ORTHOPEDIST. The West Coast's leading Occupational/Family Practice medical provider has full-time/part-time opportunities for Orthopedic Specialists in California and Washington (Seattle/Tacoma). Attractive package includes guaranteed salary, incentive bonus and benefits. Current license. Contact Thom Catlett, Vice President, 3 Corporate Plaza, #206, Newport Beach, CA 92660; call COLLECT (714) 476-8743. Join our dynamic team of professionals. Practice and live in an incomparable environment.

SURGERY, CALIFORNIA. BE/BC General/Thoracic Surgeon to join staff of 14 physician multispecialty group located in the central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to William R. Winn, MD, Kaweah Medical Group, Inc., 222 West Willow St, Visalia, CA 93291.

NORTHERN CALIFORNIA, EMERGENCY MEDICINE. Full-time positions available in the Emergency Department at the University of California, Davis, Medical Center. The University serves a large region of northern California and is a major trauma center. Emergency physicians teach and supervise medical students and housestaff (240 per year) in addition to treating patients. Emergency Department physicians also provide medical control for UCDMC Life Flight, director of base station activities, and are actively involved in trauma care. Opportunities exist for involvement in other UCD School of Medicine teaching activities. Applicants should send CV to Robert W. Derlet, MD, Chief, Division of Emergency Medicine, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817.

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FAMILY PRACTITIONERS. BE/BC for pre-paid medical group in San Francisco bay area. Send CV to James Conroy, MD, The Permanente Medical Group, Inc, 260 International Cir, San Jose, CA 95119, or call (408) 972-6339.

SOUTH DAKOTA, SIOUX FALLS. Expanding physician-owned emergency group has opening for full-time, career-oriented Emergency Physicians in South Dakota. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Send CV to PO Box 805, Cheyenne, WY 82003; or contact Donald Kougl, MD, (307) 632-1436.

MONTANA. BC Family Practitioner seeks partner with interests in Obstetrics and Rural Medicine to join busy practice in southeast Montana. Office on hospital/NH campus. First year income guarantee, relocation assistance, and other benefits. Enjoy comforts of friendly small community living and recreation that only Montana can offer! Send CV to Cynthia Lacro, PROSEARCH, 305 NE 102nd Ave, Portland, OR 97220; (800) 237-6906.

URGENT—FAMILY PRACTICE/GENERAL PRACTICE Physicians needed for excellent solo and group opportunities across the US. For information, call (602) 990-8080; or send CV in confidence to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252.

INTERNAL MEDICINE. San Francisco bay area—Immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical house staff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Cir, San Jose, CA 95119.

VENTURA (VENTURA COUNTY). Multispecialty group of 35 physicians has immediate positions available for BC/BE Cardiologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Invasive skills preferred. This is an excellent opportunity to join and grow with a successfully expanding group practice in a city chosen by *Money* magazine as one of the 10 most preferred cities to live in the USA. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Cardiologist, 2705 Loma Vista Rd, Ventura, CA 93003.

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PHYSICIANS WANTED

REGIONAL MEDICAL DIRECTORS

Southern California

CIGNA Private Practice Plan is seeking Medical Directors to supervise their Orange County and San Bernardino Regional Offices. Medical Directors provide physician back-up for utilization review and provider relations, advise plan managers regarding clinically-related issues, and provide support and education for IPA provider network.

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SUN VALLEY. INTERNIST with sub-specialty training in Gastroenterology, Neurology or Gerontology to practice sub-specialty plus primary care with quality multi-practice group. Well-equipped hospital. High quality life with outstanding year 'round recreation presents unique opportunity and professional challenge. CV and references with first letter please. Tom Peterson, PO Box 66, Sun Valley, ID 83353; (208) 622-4526.

VENTURA (VENTURA COUNTY). Multispecialty group of 35 physicians has immediate positions available for BC/BE General Internists. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist, 2705 Loma Vista Rd, Ventura, CA 93003.

GENERAL SURGEON—RARE OPPORTUNITY, BC/BE, to join internationally recognized Hernia Institute academically oriented. Send CV to Irving Lichtenstein, MD, c/o Lichtenstein Hernia Institute, 9201 Sunset Blvd, Ste 505, Los Angeles, CA 90069.

GENERAL INTERNIST OR BC FAMILY PRACTITIONER. Excellent opportunity to start or relocate in growing resort community in need of another physician. Hospital privilege a must. Will help a motivated individual. L. D. Lamothe, MD, 13120 Palm Dr, Desert Hot Springs, CA 92240.

INDUSTRIAL PHYSICIAN, California central coast. Successful Internal Medicine clinic with immediate opening for full-time MD. No nights or weekends. Internal Medicine experience desirable, Family Practice or Emergency Medicine background acceptable. Paid malpractice. Income competitive based on experience. Growing community of 80,000. Send CV to R. D. Shaw, MD, 1400 E Church St, Santa Maria, CA 93454; (805) 922-5811, ext 196.

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Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676. Western Physicians Registry, 710 Van Ness Ave. San Francisco, CA 94102.

ONCOLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Gary L. Hillman, Chief, Department of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063.

NORTHERN CALIFORNIA. Opportunity for a full-time position in a hospital-based urgent care center. Compensation is $40-45 per hour and malpractice is paid. If you are BE/BC in a primary specialty, we'd like to talk to you. Send your CV to Northern California Emergency Physicians, PO Box 214584, Sacramento, CA 95821 or call us at (916) 486-4414.

INTERNIST, BC/BE, California license. Duties will include outpatient, admissions, and in-patient care. Send résumé to Dr Susann J. Steinberg, Medical Director, Access Health Care, 26 California St, San Francisco, CA 94111.

BC/BE CARDIOLOGIST to join three invasive/noninvasive Cardiologists in practice, Portland, Oregon metropolitan area. Send CV to Number 105, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE position available in Berkeley, California. Join two female MDs, two NPs and one PA in a busy, well-established practice. Permanent position to start at mutually agreed upon date in next 18 months. Must do OB. Please write East Bay Family Practice, 2500 Milvia St, Berkeley, CA 94704 or call (415) 540-8200, Edie Silber.

GERIATRICIAN/INTERNIST. We are seeking a BC Internist with Geriatric training or certification to join a group of two to practice Geriatric Medicine, actively participate in a university-affiliated teaching program, and assist in program development. Competitive salary and excellent fringe benefits. Send CV to Gary Steinke, MD, Santa Clara Valley Medical Center, 751 S Bascom Ave, San Jose, CA 95128.

RURAL COLORADO. Eight physician group practice is seeking BC/BE Family Practitioner, Med/Peds, or Internal Medicine Physician with an interest in some Pediatric care. Competitive salary, excellent recreational opportunities in a high mountain, agricultural valley. Contact Kris Steinberg, MD, (719) 589-2562; 1710 First St, Alamosa, CO 81101.

INTERNAL MEDICINE/CARDIOLOGY BC/BE to join busy multispecialty six doctor group located in medically sophisticated small community. Easy access to Seattle, Vancouver, BC, and San Juan Islands. Send CV to Harold R. Clure, MD, Fidalgo Medical Associates, PS, 24th & M Ave, Anacortes, WA 98221; or call (206) 293-3101.

FEMALE ORIENTED PRACTICE. Great potential for Family Practitioner or Internist with emphasis on primary care of women (no OB) in a small college town, Rocky Mountain setting. Associate, join or coverage with solo Internist. Must be easy to work with and have good patient rapport. Reply to Number 104, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ENDOCRINOLOGIST BC/BE, with interest in diabetes, to assume established practice. Join a dynamic group of 10 Internists/Specialists. Outstanding initial guarantees and financial incentives. City of 50,000 is a regional referral center for 250,000. Local recreational and educational opportunities abound in this Pacific Northwest city with sunbelt climate. Send CV to Chris Nauta, Administrator, Internal Medicine Associates of Yakima, Inc, PS, 316 Holton Ave, Yakima, WA 98902.

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INTERNAL MEDICINE/FAMILY PRACTICE. Private practices available with established groups, physicians or hospital sponsored practices in Washington, Nevada, Texas, Louisiana, and Florida. For details, call Eloise Gusman, 1 (800) 535-7698 or (504) 893-4879 or send CV to PO Box 1685, Covington, LA 70434-1685.

STAFF PHYSICIAN. General/Family Practice Physician. Northern California clinic with large Medi-Cal clientele. Three physicians, two Physician Assistants. No Obstetrics. No Surgery. Near mountains, close to Sacramento, two and one-half hours to Lake Tahoe and San Francisco. Salary—$86,113 plus. Contact Jackie Travis, 938 14th St, Marysville, CA 95901; (916) 741-6259.

B/C FAMILY PRACTITIONER to join a very busy B/C physician in a well-established practice in southeastern New Mexico. Hunting, fishing, water sports, and skiing all in the area. Need a compassionate physician who likes to work. No OB. No Surgery. Partnership available after one year, if compatible. Send CV or contact Beto Gutierrez, MD, 2402 W Pierce, Ste 2A, Carlsbad, NM 88220; (505) 885-4167.

OAKLAND, CALIFORNIA. Physician BC/BE in Primary Care specialty wanted for emergency and inpatient work in east bay hospital. Must be able to handle acute care patients. Full/part-time. Base pay plus incentive. Call Dr D. Dreisbach, (415) 527-4755.

THE DEPARTMENT OF PEDIATRIC HEMATOLOGY/ONCOLOGY at Valley Children's Hospital is seeking a second, full-time hospital-based Pediatric Hematologist/Oncologist. The candidate must be BC/BE in Pediatric Hematology/Oncology. Responsibilities include patient care, teaching, and clinical research. Valley Children's Hospital is affiliated with the Children's Cancer Study Group and with the University of California, San Francisco, Fresno Pediatric Residency Program. Please contact Stan Schofield, Assistant Vice President, Medical Affairs, Valley Children's Hospital, 3151 N. Millbrook, Fresno, CA 93703.

FAMILY PRACTICE (GERIATRICS). Full-time faculty position for a BC Family Physician with a special interest in Geriatrics in an 18 resident, 7 faculty rural program affiliated with the University of California, Davis. Large clinical component, including out-patient care and supervising residents on in-patient services and in convalescent hospitals. Send inquiries with CV to J. E. Hughell, MD, Director, Family Practice Residency Program, Merced Community Medical Center, PO Box 231, Merced, CA 95340; (209) 385-7172. EOE.

NEW MEXICO NEEDS PHYSICIANS! Outstanding career opportunities available for Family Practitioners, Pediatricians, and Psychiatrists. BC/BE preferred. Both guaranteed salary and fee-for-service with incentive options are available. Contact NM Health Resources, PO Box 27650, Albuquerque, NM 87125; (505) 242-0633.

(Continued on Page 248)

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AIR FORCE

(Continued from Page 246)

PHYSICIANS WANTED

INTERNAL MEDICINE. Full-time position for a BC/BE Internist in an 18 resident, 7 faculty rural Family Medicine Program affiliated with the University of California, Davis. Duties will include supervising residents on the medical ward and in the ICU/CCU areas. Excellent salary. Send inquiries with CV to J. E. Hughell, MD, Director, Family Practice Residency Program, Merced Community Medical Center, PO Box 231, Merced, CA 95340; (209) 385-7172. EOE.

SAN DIEGO, CALIFORNIA. Hospital affiliated Primary Care group seeking additional associates. BC/BE in Family Medicine and Internal Medicine. New state-of-the-art, outpatient primary care centers. Excellent compensation package with benefits and incentive. Send CV to Medical Director, Mercy CarePoint Medical Group, 1011 Camino Del Rio South, Ste 450(Q), San Diego, CA 92108.

CALIFORNIA. Full-time Emergency Medicine attending position availabe at 233-bed teaching hospital in the heart of the San Joaquin-Sacramento River Delta. $75-$100,000 plus per year with flexible scheduling, camaraderie, and paid malpractice. Send CV to Richard Buys, MD, PO Box 1020, Stockton, CA 95201 or call (209) 468-6818. Affirmative Action/Equal Opportunity Employer.

INTERNIST. San Francisco bay area HMO seeks BC/BE Internist to join dynamic multispecialty group. Excellent salary and fringe benefits. Send CV and references to Dr Michael Getzell, Kaiser Permanente, 27400 Hesperian Blvd, Hayward, CA 94545.

FAMILY PRACTICE. Steinbeck country, BC/BE Family Practitioner to join dynamic group; includes hospital care, OB, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write: Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

HEMATOLOGIST/ONCOLOGIST, WASHINGTON STATE. BC/BE immediate opportunity to take over established practice within the Hematology/Oncology (three and one-half physician) Division of the Rockwood Clinic, a 60 member multispecialty group. Competitive salary and benefits leading to early shareholder status. Spokane (metropolitan population 350,000) offers affordable housing, excellent schools, cultural activities, and unlimited outdoor recreation. Send CV to Colleen Mooney, Recruitment Coordinator, Rockwood Clinic, TAF C-13, Spokane, WA 99220-4013; (509) 448-1304.

PEDIATRICIAN/NEONATOLOGIST AND PEDIATRICIAN. Multispecialty group seeks full-time BC/BE Pediatrician/Neonatologist and Pediatrician. Attractive compensation/benefits. Contact Don Robertson, Administrator, The Moore-White Medical Group, 266 S. Harvard Blvd, Los Angeles, CA 90004; (213) 386-8440.

FAMILY PRACTITIONER needed for rural underserved area in Hawaii. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

NEW MEXICO. Family Medical Centers, which operates three clinics in New Mexico, seeks physician specializing in Internal Medicine or Family Practice to join two full-time physicians in modern, busy clinic in Truth or Consequences, New Mexico. Clinic is well equipped and staffed to support quality medical services, with local hospital for patient admissions. No OB. Respond with résumé to Terry Smith, Administrator, 1605 A-1 El Paseo Rd, Las Cruces, NM 88001. Telephone inquiries (505) 523-2321.

PHYSICIANS WANTED

MEDICAL DIRECTOR/FAMILY PHYSICIAN. San Francisco bay area community clinic needs part-time Medical Director, flexible hours, with clinical and administrative duties. Competitive pay, malpractice provided. Contact Lisa Jafferies, 2470 Alvin Ave, #3, San Jose, CA 95121; (408) 274-8400. Start date—summer.

RADIOLOGIST, BC/BE for a 120 bed hospital. California license. General Radiology including CT, ultrasound, and nuclear medicine. Send CV to Dr H. Hashim, c/o Delano Regional Medical Center, PO Box 460, Delano, CA 93216.

OCCUPATIONAL/FAMILY PRACTICE. Extensive Occupational/Family Practice network of rapidly growing medical center in Pacific northwest has excellent full/part-time opportunities throughout California and Washington (Seattle/Tacoma). Regular hours and a balanced professional/personal lifestyle. Attractive salary/incentives/benefits/malpractice. Current state license. Prior Occupational/Family Practice experience. Join our dynamic team of professionals. Contact Director, Personnel, ReadiCare/CHEC, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (408) 737-8531, (800) 237-3234.

NEW MEXICO communities have excellent private practice opportunities available for the following specialties: BC/BE Family Practitioners, Internists, OB/GYNs, and Orthopaedic Surgeons. Financial assistance available on all opportunities. For further information, please submit CV to Bill Norris or Rita Longino, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

INTERNIST OR GENERAL PRACTITIONER, BC/BE. For Family Practice in a large, central California community and migrant health clinic located in the central San Joaquin Valley serving large Hispanic and southeast Asian medically underserved population. Competitive salary with excellent fringe benefits and paid malpractice. Send CV and inquiries to Director, Sequoia Community Health Foundation, Inc, 2790 S. Elm Ave, Fresno, CA 93706.

EMERGENCY MEDICINE, well established, Board certified group needing BC/BE Emergency Department Physician. Competitive salary plus benefits. 19,000 annual visits with high acuity. Unlimited recreational opportunities in an ideal community. Michael Parnell, MD, (509) 662-1511 or send CV to Wenatchee Emergency Physicians, PO Box 4600, Wenatchee, WA 98807.

HAVE THE BEST OF BOTH WORLDS. Rural group practice, easy commute 40 minutes to larger city. Excellent clinical practice with option for close ties to academic hospitals and part-time teaching. BC/BE Family Practitioner to join with three Family Practitioners/OB/GYN/two Pediatricians/General Surgeon, adjacent to hospital. Attractive salary/incentives. Excellent outdoor recreational opportunities. Send CV to Peter Bauer, MD, Medical Director, Family Practice Group, 255 South 1st East, Tooele, UT 84074; (801) 882-0423.

FAMILY PRACTICE. BC Family Practitioner needed in eastern Colorado community of 4,000. Call coverage and affiliation with Family Practitioner resident program in Denver available. Minor surgeries and OB involved. Two physicians recently retired leaving large gap with unlimited potential. Very attractive financial package including $80-$100,000 net guarantee, all expenses and overhead with benefits. Contact Paul Clukies, Jackson & Coker, 400 Perimeter Center Terrace, Ste 760 AFP8, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 888-0121.

CALIFORNIA. BE/BC Internist to join staff of eight Internists in 14 physician multispecialty group located in central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to Frank Kelley, MD, Kaweah Medical Group, 222 W. Willow, Visalia, CA 93291.

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DIAGNOSTIC RADIOLOGISTS. Central California HMO backed by major corporation seeks Generalist. Guaranteed competitive salary and benefit package with additional fee-for-service income opportunities. Practice in hospital with full service capabilities. All administrative needs provided by HMO. Situated in the heart of California close to major metropolitan and recreational areas. Submit CV immediately to Valley IPA, 1524 McHenry Ave, Ste 425, Modesto, CA 95350.

TWO BAY AREA (NEAR SAN FRANCISCO) SPECIALISTS need a third BC/BE in Oncology/Hematology Physician to join practice. Some Internal Medicine required. Reply with CV to PO Box 218, San Leandro, CA 94577.

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Replies to **801 S. Fifth Ave, Yuma, AZ 85364.**

VENTURA (VENTURA COUNTY). Multispecialty group of 35 physicians has immediate positions available for BC/BE Internist/Pulmonologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist/Pulmonologist, 2705 Loma Vista Rd, Ventura, CA 93003.

VENTURA (VENTURA COUNTY). Multispecialty group of 35 physicians has immediate positions available for BC/BE Family Practitioner. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Family Practitioner, 2705 Loma Vista Rd, Ventura, CA 93003.

PORTLAND, OREGON. Practice opportunities available for BC/BE Family Practitioners and General Internists. Full specialty back-up; call sharing available. Affiliate with progressive community hospital. Practice assistance includes salary guarantee, rent, relocation allowance. Send CV to Cynthia Lacro, Woodland Park Hospital, 10300 NE Hancock St, Portand, OR 97220; (503) 257-5671.

FAMILY PHYSICIANS. BC/BE, full- and part-time positions available with Obstetrics optional, to work with multispecialty group practice in the Seattle area. Attractive salary and benefits. Send CV to Pacific Health Associates, Northgate Clinic, 10416 5th Ave NE, Seattle, WA 98125, Attn: Peter Hohn, MD.

WYOMING. Immediate opening for experienced Emergency Room Physician. Competitive salary, occurrence liability insurance, excellent working conditions, new facility, low to moderate volume. Excellent outdoor recreation, hunting, fishing, one hour from nationally known ski slopes and Salt Lake City. Please call Richard Rosenthal, MD, in Evanston, Wyoming at (307) 789-3636 or write Evanston Regional Hospital, 190 Arrowhead Dr, Evanston, WY 82930.

PERFUSIONIST (CLINICAL). Minimum six months experience with BS degree Perfusion Technology and Board certified by the American Board of Cardiovascular Perfusion. Will set up and operate the heart and lung machine, monitor the intra aortic balloon device, set up pressure transducers, and perform blood gases and potassiums during surgical procedures. Please send your résumé to Pacific Cardiothoracic Surgery Group, 201 S. Alvarado St, Ste 626, Los Angeles, CA 90057. Salary: $38,800.

(Continued on Page 249)

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SITUATION WANTED

URGENT CARE PHYSICIAN. MD-JD, BCIM, 10 years Emergency Room experience, seeks full-time or part-time Urgent Care-Ambulatory Medicine or administrative practice south San Francisco bay area. Reply to Number 103, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

GENERAL PRACTITIONER, 39 years old, wants to settle in New Mexico. Family man, Christian, hard worker. Looking for locum tenens, full- or part-time position. Reply to Number 109, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

PATHOLOGIST—NEW MEXICO. Looking for locum tenens or full-time position. AP-CP, American born and trained. Contact F. Chin, MD, 1414 Erin, Monroe, LA 71201; (318) 388-2583.

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NORTHERN ARIZONA FAMILY PRACTICE. Office building and well-established solo practice for sale in Flagstaff in the peak and canyon country. Ideal location for family—good schools, university, and plenty of outdoor activities. Kirk R. Stetson, MD, 119 W Fine St, Flagstaff, AZ 86001; (602) 774-6671.

SOUTHERN CALIFORNIA FAMILY PRACTICE, established, well-equipped modern office in beautiful city of 100,000 population. PO Box 922 NPS, Thousand Oaks, CA 91320. Please send CV with inquiry.

BEAUTIFUL CENTRAL CALIFORNIA COAST. Well-established solo Family Practice with emphasis on Geriatrics/Internal Medicine. Patients and space for two physicians; limited lab and x-ray equipment on site. 12 miles to two acute care hospitals. Respondent must be BC in Family Practice or Internal Medicine. For further information, send CV to Number 107, Western Journal of Medicine, PO Box 7602. San Francisco, CA 94120-7602.

GENERAL PRACTITIONER retiring. Long-standing practice in Eureka, California. $120,000 includes real estate, office and medical equipment, accounts receivable. Terms available. Contact Stuart Rosenberg, Coldwell Banker Cutten Realty, (707) 445-8811.

ORANGE COUNTY CARDIOLOGY PRACTICE. A quality, long established practice made available by physician leaving area. Collection rate $274,740 per year in first five months of 1988. Will introduce. Terms to qualified Cardiologist. Send inquiries and CV to PO Box 5621, Orange, CA 92613-5621.

SAN DIEGO—PEDIATRIC—OB/GYN AND OTHER SPECIALTY PRACTICES AVAILABLE. Long established—doctors retiring. Various prices—low down payments. C.B.I., (619) 283-7009.

MINOR EMERGENCY AND GENERAL PRACTICE CLINIC FOR SALE—Coeur d'Alene, Idaho. Excellent lease, location, support staff easily providing for two physicians. Lab, exam, x-ray equipment. No OB, excellent specialty support; hospital practice optional. One of the nicest practices in the western United States. Box 655, Hayden Lake, ID 83835.

INTERNAL MEDICINE/ENDOCRINOLOGY PRACTICE FOR SALE. Exceptionally good income and attractive location in a northwestern state with world class outdoor activity. Reply to Number 110, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

THRIVING SURGICAL PRACTICE for sale due to untimely death of physician. Sale price negotiable. Active progressive medical community in beautiful central Washington. Excellent community hospitals. Wonderful family outdoor environment. (509) 453-5752; 1111 W. Spruce, #30, Yakima, WA 98902.

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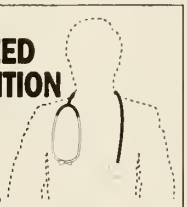

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(Continued on Page 250)

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(Continued from Page 249)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 244)

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WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

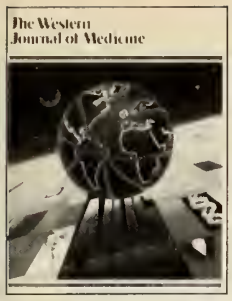
WYOMING

September 9—**Thrombolysis and Hemostatic Disorders.** West Park Hospital, Cody. Fri. Contact: Elaine Nestell, Education Director, West Park Hospital, 707 Sheridan Ave, Cody 82414. (307) 527-7501, ext 250, or 1 (800) 654-9447.

September 14-18—**Wilderness Medicine '88—Annual Meeting of the Wilderness Medical Society.** Jackson Lake Lodge, Grand Teton National Park. Wed-Sun. Contact: Diag Simpkins, Wilderness Medical Society, PO Box 397, Point Reyes Station, CA 94956. (415) 663-9107.

September 17-18—**Medicine Update.** Creighton University School of Medicine at Inn at Jackson Hole, Teton Village. Sat-Sun. 10 hrs. Contact: Division of CME, Creighton University School of Medicine, Omaha, NE 68178. (800) 548-2633. ◆

SPECIAL ISSUES



AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
Director,
Special Programme on AIDS
World Health Organization,
Geneva

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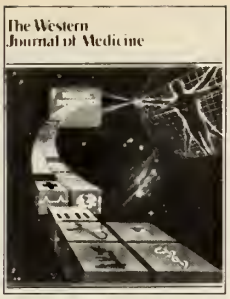

Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

—Marsden S. Blois, PhD, MD

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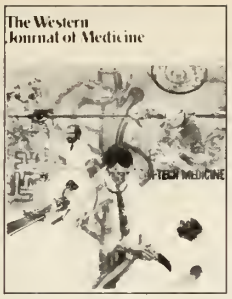

High-Tech Medicine

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

—R. Paul Robertson, MD

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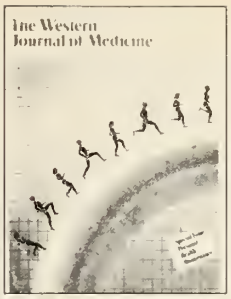

Personal Health Maintenance

The goal of this special issue is to provide an authoritative, current guide to disease prevention and health promotion. The contributors are distinguished experts in public health, epidemiology and clinical medicine.

—John H. Holbrook, MD

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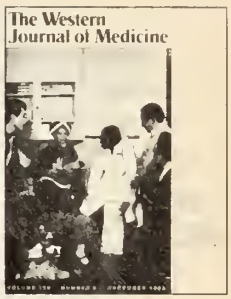

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The barriers may be great indeed when an American-trained physician undertakes to treat a patient from another ethnic or religious background. Too little attention has been given to developing better or even adequate communication across all these different cultures. The subject is of worldwide social, economic and political importance, and on a more individual and personal basis it is important in patient care.

—Malcolm S.M. Watts, MD

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In Memoriam

Arizona Medical Association

BRALLIAR, FLOYD B., Wickenburg. Died Apr 15, 1988, aged 82. Graduate of University of Tennessee College of Medicine, Memphis, 1935. Licensed in Arizona in 1936. Dr Brallar was a member of the Maricopa County Medical Society.

DALE, EDWARD C., Sun City. Died Apr 18, 1988, aged 79. Graduate of Wayne State University School of Medicine, Detroit, 1937. Dr Dale was a member of the Maricopa County Medical Society.

FELCH, HARRY J., Phoenix. Died Apr 28, 1988, aged 98. Graduate of College of Physicians and Surgeons, Los Angeles, 1916. Licensed in Arizona in 1916. Dr Felch was a member of the Maricopa County Medical Society.

GILGER, WILLIAM GRANT II, Phoenix. Died May 29, 1988, aged 68. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1944. Licensed in Arizona in 1976. Dr Gilger was a member of the Maricopa County Medical Society.

JOHNSON, ARTELL F., Mesa. Died Apr 15, 1988, aged 82. Graduate of Columbia University of Physicians and Surgeons, New York, 1937. Licensed in Arizona in 1955. Dr Johnson was a member of the Maricopa County Medical Society.

LLOYD, JOHN H., JR, Mesa. Died Apr 22, 1988, aged 61. Graduate of University of Washington School of Medicine, Seattle, 1957. Licensed in Arizona in 1965. Dr Lloyd was a member of the Maricopa County Medical Society.

MANOIL, LAZARUS, Phoenix. Died Feb 28, 1988, aged 85. Graduate of Tufts University School of Medicine, Boston, 1928. Licensed in Arizona in 1946. Dr Manoil was a member of the Maricopa County Medical Society.

PALMER, E. PAYNE, Phoenix. Died Mar 18, 1988, aged 77. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1937. Licensed in Arizona in 1938. Dr Palmer was a member of the Maricopa County Medical Society.

TAYLOR, ASHTON B., Phoenix. Died Mar 31, 1988, aged 69. Graduate of Northwestern University Medical School, Chicago, 1945. Licensed in Arizona in 1946. Dr Taylor was a member of the Maricopa County Medical Society.

California Medical Association

ABERNETHY, RODNEY E., San Mateo. Died Mar 20, 1988, aged 66. Graduate of University of California, San Francisco, 1946. Licensed in California in 1946. Dr Abernethy was a member of the San Mateo County Medical Society.

ALLEN, DOROTHY M., Oakland. Died Mar 17, 1988, aged 90. Graduate of University of California, San Francisco, 1926. Licensed in California in 1926. Dr Allen was a member of the Alameda-Contra Costa Medical Association.

ARMINO, ANTHONY, Rancho Santa Fe. Died Feb 1988, aged 41. Graduate of New Jersey College of Medicine, Newark, 1962. Licensed in California in 1963. Dr Armino was a member of the San Diego County Medical Society.

BARGER, JOHN A., San Bernardino. Died Apr 26, 1988, aged 80. Graduate of St Louis University, 1932. Licensed in California in 1951. Dr Barger was a member of the San Bernardino County Medical Society.

CALABRESE, SAVIN D., Gilroy. Died Feb 28, 1988, aged 78. Graduate of New York Medical College, 1936. Licensed in California in 1946. Dr Calabrese was a member of the Santa Clara County Medical Society.

CARLSON, ELMER O., Upland. Died Mar 15, 1988, aged 78. Graduate of University of Southern California School of Medicine, 1937. Licensed in California in 1937. Dr Carlson was a member of the San Bernardino County Medical Society.

CHAIN, JOHN S., Eureka. Died May 1, 1988, aged 82. Graduate of University of California, San Francisco, 1936. Licensed in California in 1936. Dr Chain was a member of the Humboldt-Del Norte Medical Society.

CLARK, FRED A., Riverside. Died Mar 28, 1988, aged 80. Graduate of Stanford University, 1933. Licensed in California in 1933. Dr Clark was a member of the Riverside County Medical Association.

DORIUS, GLENN R., Oakland. Died Apr 28, 1988, aged 84. Graduate of Northwestern University Medical School, Chicago, 1932. Licensed in California in 1932. Dr Dorius was a member of the Alameda-Contra Costa Medical Association.

FAUSKE, HILMER A., San Jose. Died Apr 24, 1988, aged 67. Graduate of McGill University Faculty of Medicine, Montreal, Quebec, 1955. Licensed in California in 1957. Dr Fauske was a member of the Santa Clara County Medical Society.

FRIESEN, ARNOLD R., Pasadena. Died Mar 11, 1988, aged 80. Graduate of University of Nebraska College of Medicine, Omaha, 1943. Licensed in California in 1953. Dr Friesen was a member of the Los Angeles County Medical Association.

GARNER, JAMES F., Sacramento. Died Mar 21, 1988, aged 74. Graduate of Wayne State University School of Medicine, Detroit, 1947. Licensed in California in 1948. Dr Garner was a member of the Sacramento-El Dorado Medical Society.

GREENWOOD, CHARLES F., Oakland. Died Mar 31, 1988, aged 88. Graduate of University of California, San Francisco, 1928. Licensed in California in 1928. Dr Greenwood was a member of the Alameda-Contra Costa Medical Association.

HAVEMANN, MORTON S., Palm Springs. Died Apr 14, 1988, aged 81. Graduate of University of Michigan Medical School, Ann Arbor, 1932. Licensed in California in 1933. Dr Havemann was a member of the Riverside County Medical Association.

IRION, JOHN K., Pittsburg. Died Mar 17, 1988, aged 63. Graduate of University of Rochester School of Medicine, 1947. Licensed in California in 1967. Dr Irion was a member of the Alameda-Contra Costa Medical Association.

LOEWENSTEIN, HANS G., Pittsburg. Died Mar 28, 1988, aged 73. Graduate of University of Vienna, 1937. Licensed in California in 1940. Dr Loewenstein was a member of the Alameda-Contra Costa Medical Association.

MCLEAN, EDWIN B., Berkeley. Died Feb 8, 1988, aged 81. Graduate of Harvard Medical School, Boston, 1934. Licensed in California in 1952. Dr McLean was a member of the Alameda-Contra Costa Medical Association.

MCNIECE, KENNETH J., Santa Barbara. Died Feb 26, 1988, aged 69. Graduate of Marquette University School of Medicine, Milwaukee, 1945. Licensed in California in 1950. Dr McNiece was a member of the Santa Barbara County Medical Society.

New Mexico Medical Society

BALIN, HOWARD, Belen. Died Apr 6, 1988, aged 61. Graduate of University of Pennsylvania School of Medicine, Philadelphia, 1951. Dr Balin was a member of the Valencia County Medical Society.

FELTMAN, DAVID B., Las Cruces. Died Mar 20, 1988, aged 65. Graduate of George Washington School of Medicine, Washington, DC, 1955. Licensed in New Mexico in 1958. Dr Feltman was a member of the Dona Ana County Medical Society.

KLING, HERMAN A., Albuquerque. Died May 11, 1988, aged 85. Graduate of Detroit College of Medicine and Surgery, 1931. Licensed in New Mexico in 1946. Dr Kling was a member of the Greater Albuquerque Medical Association.

Utah Medical Association

HALES, ROBERT H., Provo. Died Mar 23, 1988, aged 57. Graduate of University of Utah School of Medicine, Salt Lake City, 1957. Licensed in Utah in 1961. Dr Hales was a member of the Utah County Medical Society.

MERRILL, LOWELL GARR, Ogden. Died Apr 5, 1988, aged 70. Graduate of George Washington School of Medicine, Washington, DC. Licensed in Utah in 1952. Dr Merrill was a member of the Weber County Medical Society.

REAM, JOHN RODNEY, Salt Lake City. Died Apr 11, 1988, aged 52. Graduate of Harvard School of Medicine, 1964. Licensed in Utah in 1972. Dr Ream was a member of the Salt Lake County Medical Society.

WARD, VERNON LEROY, Ogden. Died Feb 23, 1988, aged 93. Graduate of University of Pennsylvania, Philadelphia, 1919. Licensed in Utah in 1924. Dr Ward was a member of the Weber County Medical Society.

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Alaska State Medical Association—2401 E 42nd Ave, Suite 104, Anchorage 99508. (907) 562-2662. Annual Meeting: 1989, date and place to be announced.

Arizona Medical Association, Inc—810 W Bethany Home Rd, Phoenix 85013. (602) 246-8901. Annual Meeting: 1989, date and place to be announced.

California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1989, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 15-17, 1988, Marriott City Center, Denver.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1987, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1989, date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1988, Heritage Inn, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1989, date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1989, date and place to be announced.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1987, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-23, 1988, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 15-18, 1988, Yakima.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: 1989, date and place to be announced.

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Bactrim™

(trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows

CONTRAINDICATIONS: Hypersensitivity to trimethoprim or sulfonamides; documented megaloblastic anemia due to folate deficiency; pregnancy at term and during the nursing period, infants less than two months of age.

WARNINGS: FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS.

BACTRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. Clinical signs, such as rash, sore throat, fever, arthralgia, cough, shortness of breath, pallor, purpura or jaundice, may be early indications of serious reactions. In rare instances a skin rash may be followed by more severe reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis or serious blood disorder. Perform complete blood counts frequently.

BACTRIM SHOULD NOT BE USED IN THE TREATMENT OF STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A ß-hemolytic streptococcal tonsillopharyngitis have a greater incidence of bacteriologic failure when treated with Bactrim than with penicillin.

PRECAUTIONS: *General:* Give with caution to patients with impaired renal or hepatic function, possible folate deficiency (*e.g.*, elderly, chronic alcoholics, patients on anticonvulsants, with malabsorption syndrome, or in malnutrition states) and severe allergies or bronchial asthma. In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur, frequently dose-related.

Use in the Elderly: May be increased risk of severe adverse reactions in elderly, particularly with complicating conditions, *e.g.*, impaired kidney and/or liver function, concomitant use of other drugs. Severe skin reactions, generalized bone marrow suppression (see WARNINGS and ADVERSE REACTIONS) or a specific decrease in platelets (with or without purpura) are most frequently reported severe adverse reactions in elderly. In those concurrently receiving certain diuretics, primarily thiazides, increased incidence of thrombocytopenia with purpura reported. Make appropriate dosage adjustments for patients with impaired kidney function (see DOSAGE AND ADMINISTRATION).

Use in the Treatment of Pneumocystis Carinii Pneumonia in Patients with Acquired Immunodeficiency Syndrome (AIDS): AIDS patients may not tolerate or respond to Bactrim in same manner as non-AIDS patients. Incidence of side effects, particularly rash, fever, leukopenia, elevated aminotransferase (transaminase) values, with Bactrim in AIDS patients treated for *Pneumocystis carinii* pneumonia reported to be greatly increased compared with incidence normally associated with Bactrim in non-AIDS patients.

Information for Patients: Instruct patients to maintain adequate fluid intake to prevent crystalluria and stone formation.

Laboratory Tests: Perform complete blood counts frequently, if a significant reduction in the count of any formed blood element is noted, discontinue Bactrim. Perform urinalyses with careful microscopic examination and renal function tests during therapy, particularly for patients with impaired renal function.

Drug Interactions: In elderly patients concurrently receiving certain diuretics, primarily thiazides, an increased incidence of thrombocytopenia with purpura has been reported. Bactrim may prolong the prothrombin time in patients who are receiving the anticoagulant warfarin. Keep this in mind when Bactrim is given to patients already on anticoagulant therapy and reassess coagulation time. Bactrim may inhibit the hepatic metabolism of phenytoin. Given at a common clinical dosage, it increased the phenytoin half-life by 39% and decreased the phenytoin metabolic clearance rate by 27%. When giving these drugs concurrently, be alert for possible excessive phenytoin effect. Sulfonamides can displace methotrexate from plasma protein binding sites, thus increasing free methotrexate concentrations.

Drug/Laboratory Test Interactions: Bactrim, specifically the trimethoprim component, can interfere with a serum methotrexate assay as determined by the competitive binding protein technique (CBPA) when a bacterial dihydrofolate reductase is used as the binding protein. No interference occurs if methotrexate is measured by a radioimmunoassay (RIA). The presence of trimethoprim and sulfamethoxazole may also interfere with the Jaffé alkaline picrate reaction assay for creatinine, resulting in overestimations of about 10% in the range of normal values.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Long-term studies in animals to evaluate carcinogenic potential not conducted with Bactrim. *Mutagenesis:* Bacterial mutagenic studies not performed with sulfamethoxazole and trimethoprim in combination. Trimethoprim demonstrated to be nonmutagenic in the Ames assay. No chromosomal damage observed in human leukocytes *in vitro* with sulfamethoxazole and trimethoprim alone or in combination, concentrations used exceeded blood levels of these compounds following therapy with Bactrim. Observations of leukocytes obtained from patients treated with Bactrim revealed no chromosomal abnormalities. *Impairment of Fertility:* No adverse effects on fertility or general reproductive performance observed in rats given oral dosages as high as 70 mg/kg/day trimethoprim plus 350 mg/kg/day sulfamethoxazole.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Trimethoprim and sulfamethoxazole may interfere with folic acid metabolism; use during pregnancy only if potential benefit justifies potential risk to fetus. Nonteratogenic Effects: See CONTRAINDICATIONS section.

Nursing Mothers: See CONTRAINDICATIONS section.

Pediatric Use: Not recommended for infants under two months (see INDICATIONS and CONTRAINDICATIONS sections).

ADVERSE REACTIONS: Most common are gastrointestinal disturbances (nausea, vomiting, anorexia) and allergic skin reactions (such as rash and urticaria). **FATALITIES ASSOCIATED WITH THE ADMINISTRATION OF SULFONAMIDES, ALTHOUGH RARE, HAVE OCCURRED DUE TO SEVERE REACTIONS, INCLUDING STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, FULMINANT HEPATIC NECROSIS, AGRANULOCYTOSIS, APLASTIC ANEMIA AND OTHER BLOOD DYSCRASIAS (SEE WARNINGS SECTION).**

Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, neutropenia, hemolytic anemia, megaloblastic anemia, hypoprothrombinemia, methemoglobinemia, eosinophilia. *Allergic Reactions:* Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis, allergic myocarditis, erythema multiforme, exfoliative dermatitis, angioedema, drug fever, chills, Henoch-Schoenlein purpura, serum sickness-like syndrome, generalized allergic reactions, generalized skin eruptions, photosensitivity, conjunctival and scleral injection, pruritus, urticaria and rash. Periarteritis nodosa and systemic lupus erythematosus have been reported. *Gastrointestinal:* Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin, pseudomembranous enterocolitis, pancreatitis, stomatitis, glossitis, nausea, emesis, abdominal pain, diarrhea, anorexia. *Genitourinary:* Renal failure, interstitial nephritis, BUN and serum creatinine elevation, toxic nephrosis with oliguria and anuria, crystalluria. *Neurologic:* Aseptic meningitis, convulsions, peripheral neuritis, ataxia, vertigo, tinnitus, headache. *Psychiatric:* Hallucinations, depression, apathy, nervousness. *Endocrine:* Sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents; cross-sensitivity may exist. Diuresis and hypoglycemia have occurred rarely in patients receiving sulfonamides. *Respiratory:* Pulmonary infiltrates. *Musculoskeletal:* Arthralgia, myalgia. *Miscellaneous:* Weakness, fatigue, insomnia.

DOSAGE AND ADMINISTRATION: Not recommended for use in infants less than two months of age.

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***CAPOTEN® (captopril tablets) may be used as initial therapy only for patients with normal renal function in whom the risk of neutropenia/agranulocytosis is relatively low (1 out of over 8,600 in clinical trials). Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white cells or immune response. Evaluation of hypertensives should always include assessment of renal function. Overall, the most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited. See INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS in the brief summary on the adjacent page.**

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1. Croog SH, Levine S, Testa MA, et al: The effects of antihypertensive therapy on the quality of life. N Engl J Med 314(26):1657-1664, 1986.
2. Data on file, University of Connecticut.

SQUIBB

Means a feeling of well-being.

Well-being—a feeling difficult to describe when it's present; easy to spot when it's gone. CAPOTEN improved hypertensive patients' sense of general well-being.[1] CAPOTEN had a positive effect on patients' vitality and general health. In fact, all measures of well-being studied showed a trend toward improvement.[2]

These data are based on a multicenter, randomized, 24-week study of 626 mild-to-moderate hypertensive male patients with normal renal function, 181 of whom received captopril.

CAPOTEN—things are looking up for patients who need to keep their blood pressure down.

OF LIFE

THE

CAPOTEN®

(captopril tablets)

DIFFERENCE

QUALITY OF LIFE

THE CAPOTEN® (captopril tablets) DIFFERENCE

CAPOTEN® TABLETS

Captopril Tablets

INDICATIONS: Hypertension—CAPOTEN (captopril) is indicated for the treatment of hypertension. Consideration should be given to the risk of neutropenia/agranulocytosis (see WARNINGS). CAPOTEN may be used as initial therapy for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for those who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations. CAPOTEN is effective alone and in combination with other antihypertensive agents, especially thiazide-type diuretics.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

CONTRAINDICATIONS: CAPOTEN is contraindicated in patients who are hypersensitive to this product.

WARNINGS: Neutropenia/Agranulocytosis—Neutropenia (< 1000/mm³) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis. The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed. In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk in clinical trials was about 1 per 500. Doses were relatively high in these patients, particularly in view of their diminished renal function. In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7% of patients in clinical trials. While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. Of reported cases, about half had serum creatinine ≥1.6 mg/dL and more than 75% received procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

Neutropenia has appeared usually within 3 months after starting therapy, associated with myeloid hypoplasia and frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen. Neutrophils generally returned to normal in about 2 weeks after captopril was discontinued, and serious infections were limited to clinically complex patients. About 13% of the cases of neutropenia have ended fatally, but almost all fatalities were in patients with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors. **Evaluation of the hypertensive or heart failure patient should always include assessment of renal function.** If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately 2-week intervals for about 3 months, then periodically. In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after an assessment of benefit and risk, and then with caution. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, perform white cell counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count < 1000/mm³) withdraw captopril and closely follow the patient's course.

Proteinuria: Total urinary proteins > 1 g per day were seen in about 0.7% of patients on captopril. About 90% of affected patients had evidence of prior renal disease or received high doses (> 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients. Since most cases of proteinuria occurred by the 8th month of therapy with captopril, patients with prior renal disease or those receiving captopril at doses > 150 mg per day, should have urinary protein estimates (dip-stick on 1st morning urine) before therapy, and periodically thereafter.

Hypotension: Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]). In heart failure, where the blood pressure was either normal or low, transient decreases in mean blood pressure > 20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function*—Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine > 20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis due to decreased afterload reduction. *Surgery/Anesthesia*—If hypotension occurs during surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension—Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st hour after administration of the initial of captopril dose in patients on diuretics, especially those recently placed on diuretics, and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy or by initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least 1 hour after the initial dose.

Agents Having Vasodilator Activity—In heart failure patients, vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Use potassium-containing salt substitutes with caution.

Inhibitors of Endogenous Prostaglandin Synthesis—Indomethacin and other nonsteroidal anti-inflammatory agents may reduce the antihypertensive effect of captopril, especially in low renin hypertension.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Pregnancy: Category C: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects and craniofacial malformations were observed in rabbits. Therefore, captopril should be used during pregnancy, or for patients likely to become pregnant, only if the potential benefit outweighs the potential risk to the fetus. Captopril crosses the human placenta.

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. CAPOTEN (captopril) should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal—About 1 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis has occurred (see WARNINGS). Anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic—Rash, (usually maculopapular, rarely urticarial), often with pruritus, and sometimes with fever and eosinophilia, in about 4 to 7 of 100 patients (depending on renal status and dose), usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 1000 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema has been reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension may occur; see WARNINGS and PRECAUTIONS [Drug Interactions] for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, cough, alopecia, paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice, and hepatocellular injury with or without secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertension patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern is correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg and 50 mg also available in bottles of 1000), and in UNIMATIC® unit-dose packs of 100 tablets. (J3-658J)

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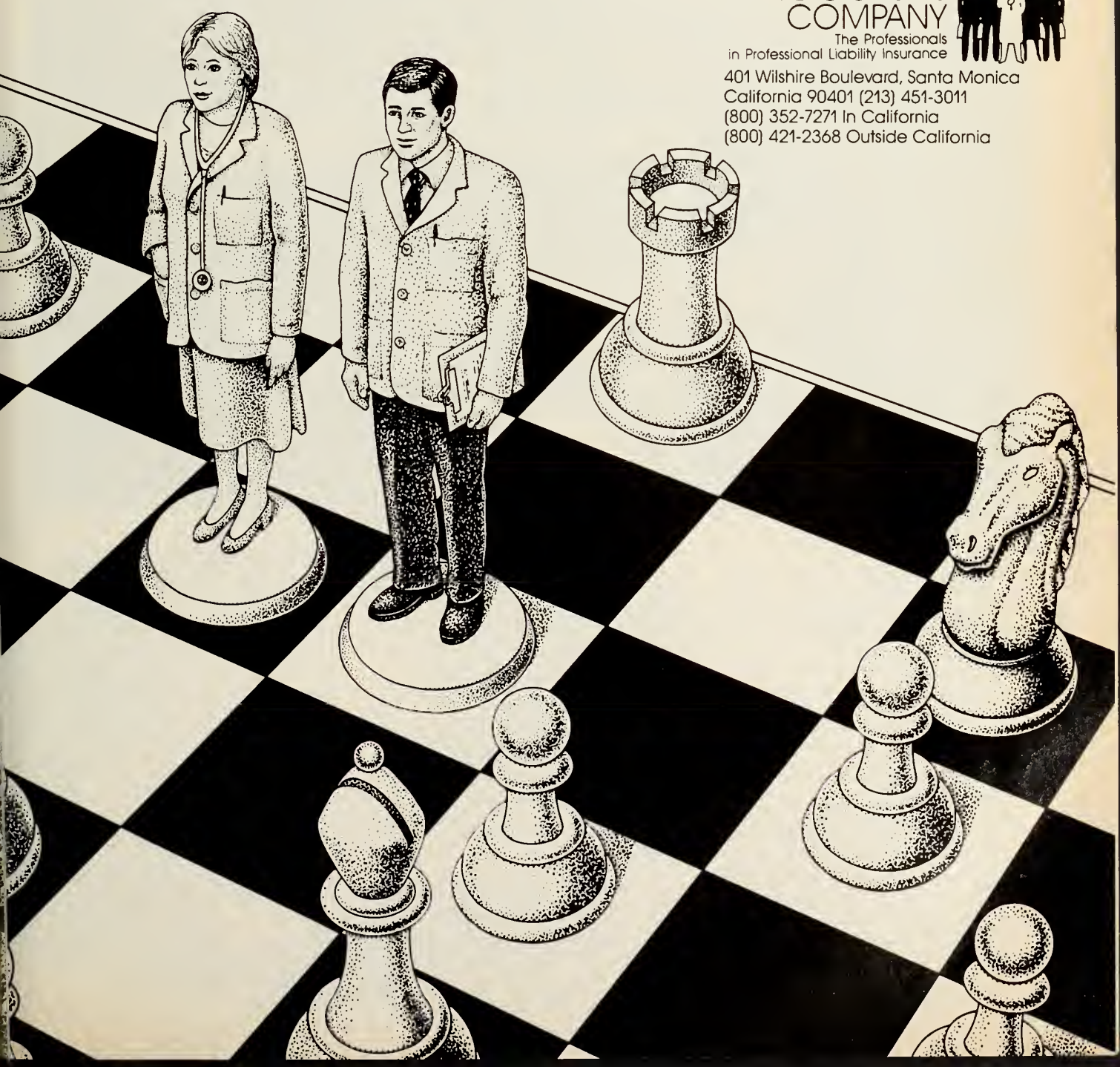

A NEW H_2 Antagonist

AXID® 300mg

nizatidine

Effective once-nightly
duodenal ulcer therapy available in a

Unique Convenience Pak

for better patient compliance

AXID®
nizatidine capsules

Brief Summary. Consult the package insert for prescribing information.

Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within four weeks.

Axid is indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg h.s. after healing of an active duodenal ulcer. The consequences of continuous therapy with Axid for longer than one year are not known.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists.

Precautions: *General*—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy.

2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency.

3. Pharmacokinetic studies in patients with hepatorenal syndrome have not been done. Part of the dose of nizatidine is metabolized in the liver. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine.

Drug Interactions—No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement compared to concurrent controls, and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid.

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay.

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect; but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights. On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus. There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating rats. Pups reared by treated lactating rats had depressed growth rates. Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers.

Pediatric Use—Safety and effectiveness in children have not been established.

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Elderly patients may have reduced renal function.

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations. Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo. Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0.2%), urticaria (0.5% vs <0.01%), and somnolence (2.4% vs 1.3%) were significantly more common in the nizatidine group. A variety of less common events was also reported, it was not possible to determine whether these were caused by nizatidine.

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine. In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients. All abnormalities were reversible after discontinuation of Axid.

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects.

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid. Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo. Rare reports of gynecomastia occurred.

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs.

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported.

Overdosage: There is little clinical experience with overdosage of Axid in humans. If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis for four to six hours increased plasma clearance by approximately 84%.

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous LD_{50} values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively. PV 2091 AMP [041288]

Axid® (nizatidine, Lilly)

Lilly

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During the first months of life, Vi-Flor® vitamin-fluoride supplements begin to enhance tooth morphology,[1] increase enamel hardness, and promote mineralization of unerupted teeth[2]—all while providing recommended minimum daily amounts of selected vitamins.

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INDICATIONS AND USAGE: Prophylaxis of vitamin deficiencies and dental caries in children and adults when fluoride of water supply does not exceed 0.7 ppm.[1,2,3] And, in the case of TRI-VI-FLOR® 0.25 mg Drops with Iron and POLY-VI-FLOR® Drops and Chewable Tablets with Iron, prophylaxis against iron deficiencies. Note: VI-FLOR Drops do not contain folic acid because the vitamin is not stable in liquid form.

PRECAUTIONS: Do not exceed recommended dose or give concurrently with other medications containing significant amounts of fluoride. Prolonged excessive fluoride intake may cause dental fluorosis. All VI-FLOR® with Iron products: as with all products containing iron, parents should be warned against excessive dosage. The bottle should be kept out of reach of children.

Keep all VI-FLOR with Iron products tightly closed and away from direct light.

VI-FLOR Drops should be dispensed in the original plastic container, since contact with glass leads to instability and precipitation.

ADVERSE REACTIONS: Allergic rash has rarely been reported.

DOSAGE AND ADMINISTRATION:
Supplemental Fluoride Dosage Schedule (mg/day)*

Age	Concentration of Fluoride in Drinking Water (ppm)		
	<0.3	0.3-0.7	>0.7
2-wk-2 yr**	0.25	0	0
2-3 yr	0.5	0.25	0
3-16 yr	1.0	0.5	0

*From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride Supplementation: Revised Dosage Schedule. *Pediatrics* 63(1):150-152, 1979
**The Committee favors initiating fluoride supplementation shortly after birth in breast-fed infants (0.25 mg F/day). In formula-fed infants, fluoride supplementation should be according to the fluoride content of the water used to prepare formula

PRODUCT	FORM	SIZE	FLUORIDE mg/dose
POLY-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
POLY-VI-FLOR 0.25 mg	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.25 mg with Iron	Tablets	Bottle of 100	0.25
POLY-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg with Iron	Drops	50 ml Bottle	0.5
POLY-VI-FLOR 0.5 mg	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 0.5 mg with Iron	Tablets	Bottle of 100	0.5
POLY-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0
POLY-VI-FLOR 1.0 mg with Iron	Tablets	Bottle of 100	1.0
TRI-VI-FLOR 0.25 mg	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.25 mg with Iron	Drops	50 ml Bottle	0.25
TRI-VI-FLOR 0.5 mg	Drops	50 ml Bottle	0.5
TRI-VI-FLOR 1.0 mg	Tablets	Bottle of 100	1.0

REFERENCES:
1. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Four Years. *J Dentistry for Children* 34:439-443 (Nov) 1967.
2. Hennon DK, Stookey GK and Muhler JC: The Clinical Anticariogenic Effectiveness of Supplementary Fluoride-Vitamin Preparations—Results at the End of Five and a Half Years. *Pharmacology and Therapeutics in Dentistry* 1:1-6 (Oct) 1970.
3. Hennon DK, Stookey GK and Muhler JC: Prophylaxis of Dental Caries: Relative Effectiveness of Chewable Fluoride Preparations With and Without Added Vitamins. *J Pediatrics* 80:1018-1021 (June) 1972.

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(For complete details, please consult full prescribing information.)

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In Memoriam

Arizona Medical Association

Goss, Martha D., Tucson. Died Jul 14, 1988, aged 80. Graduate of Rush Medical College, Chicago, 1934. Licensed in Arizona in 1954. Dr Goss was a member of the Pima County Medical Society.

Kovar, Jerome Dean, Prescott. Died Jun 15, 1988, aged 73. Graduate of Creighton University School of Medicine, Omaha, 1943. Licensed in Arizona in 1953.

Shill, Wilson T., Tempe. Died Jun 29, 1988, aged 61. Graduate of University of Utah College of Medicine, Salt Lake City, 1964. Licensed in Arizona in 1965. Dr Shill was a member of the Maricopa County Medical Society.

California Medical Association

Manson, Robert M., San Jose. Died Mar 28, 1988, aged 68. Graduate of Stanford University, 1945. Licensed in California in 1945. Dr Manson was a member of the Santa Clara County Medical Society.

Maxwell, Harvey C., Santa Ana. Died Feb 24, 1988, aged 87. Graduate of University of Minnesota, 1925. Licensed in California in 1935. Dr Maxwell was a member of the Orange County Medical Association.

Pedersen, Lars A., Richmond. Died Jan 27, 1988, aged 75. Graduate of Georgetown University Medical School, Washington, DC, 1940. Licensed in California in 1941. Dr Pedersen was a member of the Alameda-Contra Costa Medical Association.

Reich, Thomas, Oakland. Died Jan 24, 1988, aged 79. Graduate of Stanford University, 1937. Licensed in California in 1938. Dr Reich was a member of the Alameda-Contra Costa Medical Association.

Sanseau, Carlos A., Walnut Creek. Died Feb 14, 1988, aged 44. Graduate of Faculty of Medicine, University of Buenos Aires, Argentina, 1968. Licensed in California in 1974. Dr Sanseau was a member of the Alameda-Contra Costa Medical Association.

Schnell, Edward B., Santa Clara. Died Feb 22, 1988, aged 61. Graduate of Northwestern University Medical School, Chicago, 1951. Dr Schnell was a member of the Santa Clara County Medical Society.

Smith, John Vernon, Martinez. Died Jan 31, 1988, aged 82. Graduate of University of Iowa School of Medicine, Iowa City, 1931. Licensed in California in 1944. Dr Smith was a member of the Alameda-Contra Costa Medical Association.

Stewart, Harry L., Jr, Santa Barbara. Died Mar 3, 1988, aged 81. Graduate of Jefferson Medical College, Philadelphia, 1934. Licensed in California in 1951. Dr Stewart was a member of the Santa Barbara County Medical Society.

Stone, Vean M., Riverside. Died Feb 14, 1988, aged 74. Graduate of University of Nebraska, Omaha, 1938. Licensed in California in 1946. Dr Stone was a member of the Riverside County Medical Association.

Vetter, Thomas H., Anaheim. Died Feb 1988, aged 74. Graduate of Hahnemann University School of Medicine, Philadelphia, 1942. Licensed in California in 1950. Dr Vetter was a member of the Orange County Medical Association.

Whitten, Richard H., Sr, Fresno. Died Mar 21, 1988, aged 72. Graduate of University of California, San Francisco, School of Medicine, 1946. Licensed in California in 1946. Dr Whitten was a member of the Fresno-Madera Medical Society.

Williams, Alvin B., San Jose. Died Mar 17, 1988, aged 80. Graduate of University of Minnesota, 1935. Licensed in California in 1935. Dr Williams was a member of the Santa Clara County Medical Society.

Wilson, James A., Hayward. Died Feb 18, 1988, aged 83. Graduate of University of Texas Medical School, 1939. Licensed in California in 1948. Dr Wilson was a member of the Alameda-Contra Costa Medical Association.

Wong, Oakland, San Jose. Died Feb 27, 1988, aged 51. Graduate of University of Oregon School of Medicine, Portland, 1962. Licensed in California in 1963. Dr Wong was a member of the Santa Clara County Medical Society.

New Mexico Medical Society

Kenney, Bergere A., Santa Fe. Died Jun 30, 1988, aged 68. Graduate of Northwestern University, Chicago, 1945. Licensed in New Mexico in 1948. Dr Kenney was a member of the Santa Fe County Medical Society.

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†See Warnings and Precautions.

Please see brief summary of prescribing information on the next page.

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Sig: tid

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BRIEF SUMMARY
Professional Use Information

CARDIZEM®
(diltiazem HCl)
30 mg, 60 mg, 90 mg and 120 mg Tablets

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by x-ray on admission

WARNINGS

1. **Cardiac Conduction**. CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1,243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem
2. **Congestive Heart Failure**. Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients
3. **Hypotension**. Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension
4. **Acute Hepatic Injury**. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGDT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions have been reversible upon discontinuation of drug therapy. The relationship to CARDIZEM is uncertain in most cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of CARDIZEM. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interaction. Due to the potential for additive effects, caution and careful titration are warranted in patients receiving CARDIZEM concomitantly with any agents known to affect cardiac contractility and/or conduction. (See WARNINGS.)

Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

As with all drugs, care should be exercised when treating patients with multiple medications. CARDIZEM undergoes biotransformation by cytochrome P-450 mixed function oxidase. Coadministration of CARDIZEM with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio or in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered CARDIZEM to maintain optimum therapeutic blood levels.

Beta-blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of CARDIZEM (diltiazem hydrochloride) concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted. (See WARNINGS.)

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a one-week course of cimetidine at 1,200 mg per day and diltiazem 60 mg per day. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system probably responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of CARDIZEM with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing CARDIZEM therapy to avoid possible over- or under-digitalization. (See WARNINGS.)

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women, therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of CARDIZEM is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences as well as their frequency of presentation are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%). In addition, the following events were reported infrequently (less than 1%):

Cardiovascular	Angina, arrhythmia, AV block (first degree), AV block (second or third degree—see conduction warning), bradycardia congestive heart failure, flushing, hypotension, palpitations, syncope.
Nervous System	Amnesia, depression, gait abnormality, hallucinations, insomnia, nervousness, paresthesia, personality change, somnolence, tinnitus, tremor.
Gastrointestinal	Anorexia, constipation, diarrhea, dysgeusia, dyspepsia, mild elevations of alkaline phosphatase, SGDT, SGPT, and LDH (see hepatic warnings), vomiting weight increase.
Dermatologic	Petechiae, pruritus, photosensitivity urticaria
Other:	Amblyopia, CPK elevation, dyspnea, epistaxis, eye irritation, hyperglycemia, nasal congestion, nocturia, osteoarticular pain, polyuria, sexual difficulties.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, gingival hyperplasia, erythema multiforme, and leukopenia. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

Issued 3/1/88

See complete Professional Use Information before prescribing.

References: 1. Schroeder JS: Mod Med 1982;50(Sept):94-116. **2.** Cohn PF, Braunwald E: Chronic ischemic heart disease, in Braunwald E (ed): Heart Disease: A Textbook of Cardiovascular Medicine, ed 2. Philadelphia, WB Saunders Co, 1984, chap 39. **3.** O'Rourke RA: Am J Cardiol 1985;56:34H-40H. **4.** McCall D, Walsh RA, Frohlich ED, et al: Curr Probl Cardiol 1985;10(8):6-80. **5.** Frishman WH, Charlap S, Goldberger J, et al: Am J Cardiol 1985;56:41H-46H. **6.** Shapiro W: Consultant 1984;24(Dec):150-159. **7.** O'Hara MJ, Khurmi NS, Bowles MJ, et al: Am J Cardiol 1984;54:477-481. **8.** Strauss WE, McIntyre KM, Parisi AF, et al: Am J Cardiol 1982;49:560-566. **9.** Feldman RL, Pepine CJ, Whittle J, et al: Am J Cardiol 1982;49:554-559

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ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

October 21-23—**Diagnosis and Management of Respiratory Diseases.** The Boulders, Scottsdale. Fri-Sun. Contact: Medical Education Resources, 1 (800) 421-3756.

November 10-12—**First Annual Spinal Workshop.** The Pointe at Squaw Peak, Phoenix. Thurs-Sat. Contact: Toby Jardine, Barrow Neurological Institute, (602) 285-3178 or 1 (800) BARROW-1.

November 11-13—**17th Annual Seminar—Musculoskeletal Radiology.** Marriott's Camelback Inn, Scottsdale. Fri-Sun. Contact: Alex Newman, MD, Department of Radiology, Maricopa Medical Center, (602) 267-5361.

December 3-4—**Annual Meeting of the Arizona Chapter of the American College of Surgeons.** Rancho de los Caballeros, Wickenburg. Sat-Sun. Contact: Lee Ansel, MD, Program Chairman, (602) 251-3131.

February 22-24—**12th Annual Mid-Winter Symposium in OB/GYN.** Scottsdale Hilton Hotel, Scottsdale. Wed-Fri. Contact: Phoenix OB/GYN Society, (602) 266-6321.

March 4-8—**Third Annual Magnetic Resonance Imaging Conference.** Camelback Inn Resort, Scottsdale. Sat-Wed. Contact: Kevin King, Barrow Neurological Institute, (602) 285-3956.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W. Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (602) 626-6707.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 541-0900. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY

October 14—**18th Course on Allergy and Immunology.** Pacific Presbyterian Medical Center at San Francisco. Fri. Contact: Herbert S. Kaufman, MD, PPMC, 2340 Clay St, Rm 313, San Francisco 94115. (415) 923-3441.

November 10—**Advances in Diagnosis and Treatment of Allergic Diseases.** UCSF at Le Meridien Hotel, San Francisco. Thurs. 8 hrs. $100. Contact: UCSF.

ANESTHESIOLOGY

September 30-October 1—**Anesthesia Practice 1988.** Anesthesiology Educational Foundation. Fri-Sun. 11 hrs. Contact: AEF, PO Box 24230, Federal Building, Los Angeles 90024. (213) 825-0736.

October 16-21—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui Hotel, Maui. Sun-Fri. 20 hrs. $325/$375. Contact: CSA, 1065 Hilldale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 15-20—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologist at Sheraton Kauai Hotel, Poipu Beach, Kauai. Sun-Fri. 20 hrs. $325. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3020.

January 29-February 3—**Clinical Update in Anesthesiology.** Tucson Hospitals Medical Education Program at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sun-Fri. Contact: Murray G. Atnikov, MD, c/o Box F110-63, Blaine, WA 98230. (604) 874-5291.

February 4-10—**Clinical Update in Anesthesiology.** Biennial Western Conference on Anesthesiology at Stouffer's Wailea Beach Resort, Maui, Hawaii. Sat-Sun. Contact: Murray G. Atnikov, MD. (604) 874-5291.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Boulevard, Sacramento 95817. (916) 453-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Medical Center, 2801 Atlantic Avenue, Long Beach 90801-1428. (213) 595-3811, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7186.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3713.

UCSF: University of California, San Francisco
Contact: Robert Maggio, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (213) 224-7051.

(Continued on Page 276)

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(Continued from Page 274)

CARDIOLOGY

October 21-22—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Hyatt on Union Square, San Francisco. Fri-Sat. $295. Contact: Deborah Wilderson, MER, 5808 S. Rapp St, Ste 202, Littleton, CO 80120. (800) 421-3756.

DERMATOLOGY

October 14-16—**7th Postgraduate Course in Medical Mycology (Dermatology).** UCSF at San Francisco. Fri-Sun. Contact: UCSF.

EMERGENCY MEDICINE

October 10-14—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium I & Optional Advanced Emergency Procedures Laboratory.** UCSD at Catamaran Resort Hotel, San Diego. Mon-Fri. 32 hrs. $450. Contact: UCSD.

October 21-23—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

November 4-6—**Management of the Child With Head Injury.** Children's Hospital Oakland at Monterey Conference Center and Hotel Pacific, Monterey. Fri-Sun. 12 hrs. $280. Contact: Kim Leadon, Continuing Medical Education, Children's Hospital Oakland, 747-52nd St, Oakland 94609. (415) 428-3021.

November 7-10—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Imperial Palace, Las Vegas, Nevada. Mon-Thurs. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

November 14-18—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium III & Optional Advanced Emergency Procedures Laboratory.** UCSD at Hanalei Hotel, Hawaii. Mon-Fri. 32 hrs. $450. Contact: UCSD.

December 4-9—**Current Concepts in Emergency Care.** Institute for Emergency Medical Education at Royal Lahaina Resort, Maui, Hawaii. Sun-Fri. 25 hrs. Contact: Georgine Elich, Kailani World Travel, 4192 Meridian Ave, Bellingham, WA 98226. (800) 524-5264.

December 5-9—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposium II & Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. 32 hrs. $450. Contact: UCSD.

January 16-20—**Postgraduate Institute for Emergency and Primary Care Physicians and Optional Advanced Emergency Procedures Laboratory.** UCSD at San Diego Marriott Hotel & Marina. Mon-Fri. $450. Contact: UCSD.

January 26-30—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Maui Marriott, Maui, Hawaii. Thurs-Mon. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

January 27-29—**Advanced Cardiac Life Support.** CPR Seminars at Ralph K. Davies Medical Center, San Francisco. Fri-Sun. Contact: CPR Seminars, 833 Market St, Ste 421, San Francisco 94103. (415) 543-7282.

February 19-24—**Emergency Medicine.** UCD. Sun-Fri. Contact: UCD.

March 2-5—**Emergency Medicine: A Critical Appraisal—Series II.** Emergency Medical Abstracts at Sheraton Universal, Los Angeles. Thurs-Sun. 20 hrs. $375. Contact: Bob Coswill, Premier Conference Group, 5010 Edenhurst Ave, Los Angeles 90039. (800) 243-5976.

March 20-24—**Postgraduate Institute for Emergency and Primary Care Physicians, Symposia I, II, III and Optional Advanced Emergency Procedures Laboratory.** UCSD. Mon-Fri. $450. Contact: UCSD.

INTERNAL MEDICINE

September 15-18—**Medical Acupuncture for Physicians: Part I.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. Thurs-Sun. 200 hrs. $3,200. Contact: UCLA.

September 22-24—**International Symposium on Medical Virology.** UCI at Ramada Renaissance Hotel, San Francisco. Thurs-Sat. Contact: Dr Luis M. de la Maza, Department of Pathology, Rt 84, UCI Medical Center, 101 City Drive S., Orange, 92668. (714) 634-6868.

October 4-7—**Rheumatology and Clinical Immunology.** UCSF at Stanford Court, San Francisco. Tues-Fri. 19 hrs. $395. Contact: UCLA.

October 14-15—**13th Annual Clinical Neurosciences Symposium.** Dominican Neurologic Institute at Chaminade Conference Center, Santa Cruz. Fri-Sat. 11 hrs. $350. Contact: Karen Rickenbach, Dominican Hospital, 1555 Soquel Dr, Santa Cruz 95065. (408) 462-7562.

November 3-5—**New Directions in Anti-viral Chemotherapy.** UCSF at Hyatt on Union Square, San Francisco. Thurs-Sat. $100. Contact: UCSF.

November 7-9—**12th Annual Cancer Symposium.** Scripps Memorial Cancer Hospital at Sheraton Harbor Island Hotel E, San Diego. Mon-Wed. 21 hrs. $390. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

November 9—**Gastroenterology Symposium.** Enloe Hospital and Chico Community Hospital at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital, Medical Staff. (916) 891-7300, ext 7375.

November 11-14—**The Spine: Current Concepts of Diagnosis and Treatment.** The Spine Study Group at Marriott Desert Springs Resort, Palm Springs. Fri-Mon. $250. Contact: The Spine Study Group, PO Box 33185, San Diego 92103. (619) 692-9115.

November 16—**Common Musculoskeletal Problems.** VA Medical Center Sepulveda. 6 hrs. Contact: Arun J. Mehta, Rehabilitation Medicine Service (117), VA Medical Center, Sepulveda 91343. (818) 891-2473.

December 1-2—**Recent Advances in Occupational Cancer.** UCSF at Hotel Meridien, San Francisco. Thurs-Fri. $220. Contact: UCSF.

December 30-January 8—**Medical Acupuncture for Physicians: Part II.** UCLA at Bay View Plaza Holiday Inn, Santa Monica. 10 days. 200 hrs. $3,200. Contact: UCLA.

January 6-7—**6th Annual Reider Laser Symposium—Urology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 23-26—**Neurology Update.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Mon-Thurs. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 25-27—**12th Annual: Neurology for Non-Neurologists.** UCSD at Holiday Inn Embarcadero, San Diego. Wed-Fri. 21 hrs. $400. Contact: Edith S. Bookstein, NNN, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 8-10—**Clinical Laboratory Molecular Analysis.** Scripps Clinic and Research Foundation at San Diego Princess Resort, San Diego. Wed-Fri. 21 hrs. Contact: Bonny Mower, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

February 20-22—**Clinical Hematology and Oncology: 1989.** Scripps Clinic and Research Foundation at San Diego Princess Resort. Mon-Wed. 24 hrs. $350. Contact: Bonny A. Mower, Conference Coordinator. (619) 457-8556.

OB/GYN

November 10-13—**Current Issues in Perinatal Medicine.** UCI at Marriott's Rancho Las Palmas Resort, Palm Springs. Thurs-Sat. Contact: UCI.

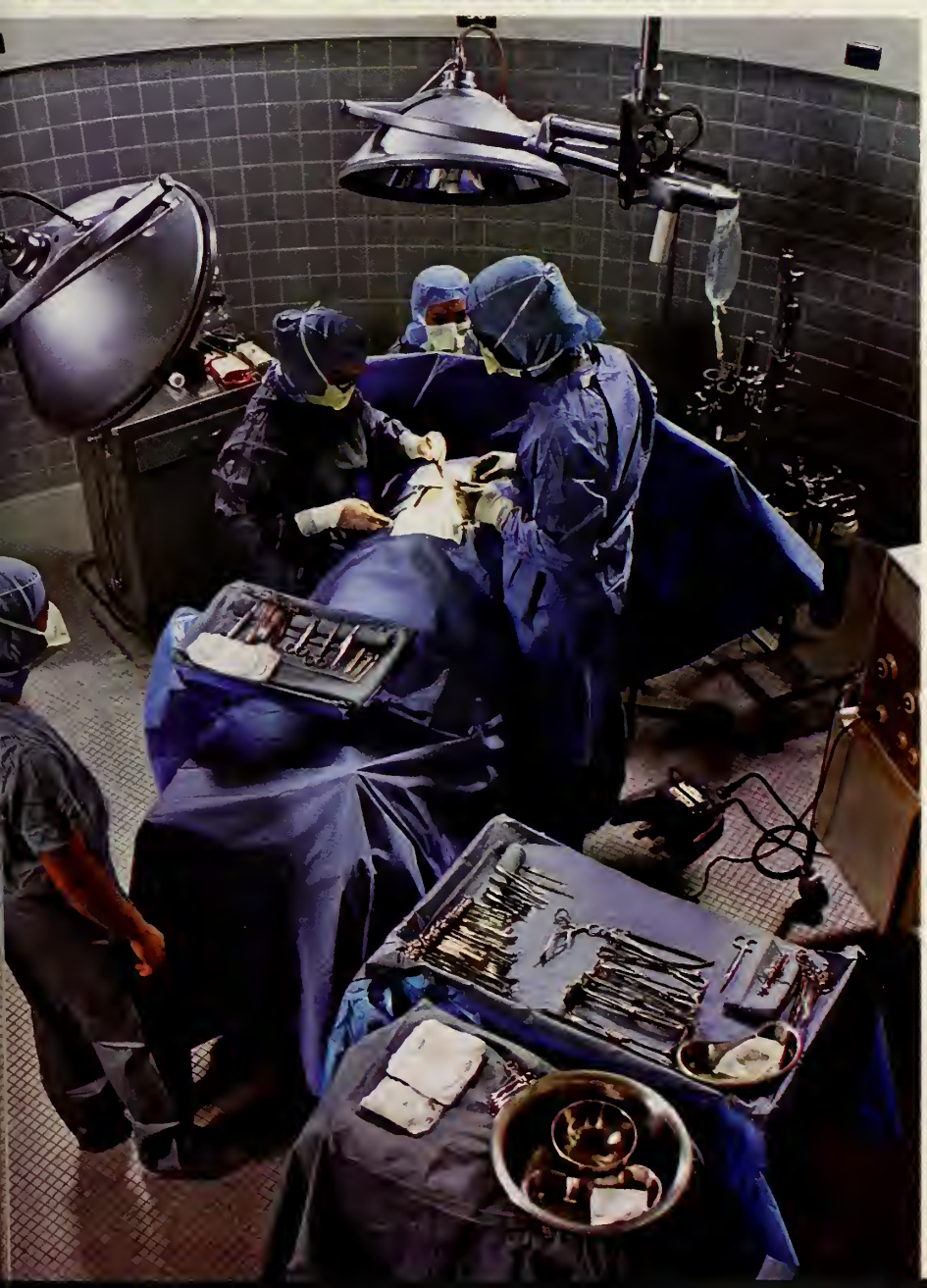
November 12—**Infertility Update V.** Scripps Clinic and Research Foundation Amphitheater, La Jolla. Sat. 7 hrs. $110. Contact: Bonny Mower, Box 400S, Dept of Academic Affairs, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

November 13-19—**11th Annual Review Course in Clinical Obstetrics & Gynecology.** The Center for Health Education at Westin South Coast Plaza Hotel, Costa Mesa. Sun-Sat. Contact: The Center for Health Education, 2081 Atlantic Ave., PO Box 1428, Long Beach. 90801-1428. (213) 595-3811.

January 6-7—**6th Annual Reider Laser Symposium—Gynecology.** Center for Health Education, Long Beach. Fri-Sat. Contact: UCI.

January 29-February 2—**Ob/Gyn.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

(Continued on Page 278)



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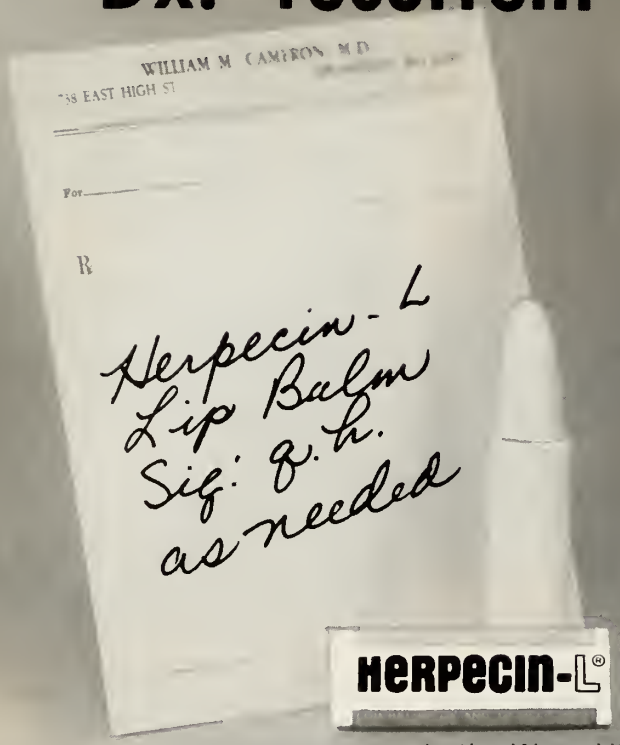

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CONTINUING MEDICAL EDUCATION

(Continued from Page 276)

ORTHOPEDICS

October 21-23—**Office Orthopedics for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess. Fri-Sun. 20 hrs. $395. Contact: Jacqueline Shiller, Medical Education, PO Box 84296, San Diego 92138. (619) 223-2997.

January 21-28—**Orthopaedic Emergencies.** Scripps Memorial Hospital Encinitas at Kona Surf Resort, Kona, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 12—**1989 Interim Meeting of American Orthopaedic Society of Sports Medicine.** American Orthopaedics Society for Sports Medicine at Las Vegas, Nevada. Sun. Contact: AOSSM, 70 W Hubbard St, Ste 202, Chicago, IL 60610. (312) 644-2623.

PEDIATRICS

September 24-25—**45th Annual Brennemann Memorial Lectures.** Los Angeles Pediatric Society at Los Angeles Hilton Hotel. Sat-Sun. $175. Contact: Los Angeles Pediatric Society, PO Box 2022, Inglewood 90305.

October 13-16—**Advanced Fetal Heart Rate Monitoring.** Center for Health Education at Embassy Suites, Napa. Thurs-Sun. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

October 15-20—**American Academy of Pediatrics Annual Session.** AAP. Sat-Thurs. Contact: AAP, 1801 Hinman Ave., Evanston, IL 60201.

October 21-22—**A Symposium on Clinical Problems in Child Neurology.** UCSF at Hyatt Regency Hotel, San Francisco. Fri-Sat. 11 hrs. $215. Contact: UCSF.

October 22-29—**13th Annual Pediatrics for the Practitioner: A Pediatric Symposium.** Center for Health Education at Mauna Kea Beach Hotel, Hawaii. One week. Contact: The Center for Health Education, PO Box 1428, Long Beach 90801-1428.

November 4-6—**Current Advances in Pediatrics.** Orange County Psychiatric Society at Disneyland Hotel, Anaheim. Fri-Sun. 14 hrs. Contact: OCPS California Chapter 4, PO Box 1297, Orange 92668. (714) 978-2415.

December 3—**7th Annual Binational Pediatric Conference.** Children's Hospital San Diego at Mercy Hospital Educational Center, San Diego. Sat. 7 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 27-29—**27th Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation at Los Angeles Airport Marriott. Fri-Sun. 15 hrs. $225. Contact: Katherine Barky, MD, Childrens Hospital, PO Box 54700, Los Angeles 90054.

February 10-12—**Current Concepts in Pediatric Medicine.** Children's Hospital & Health Center at Marriott Hotel, San Diego. Wed-Fri. Contact: Children's Hospital & Health Center, Continuing Medical Education Office, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 20-22—**Pediatrics Update: 1989.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

November 18-20—**34th Annual Group Therapy Symposium.** UCSF. Fri-Sun. Contact: UCSF.

January 22-27—**15th Annual Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. Contact: UCD.

(Continued on Page 283)

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Zantac® Tablets

ranitidine HCl/Glaxo

150 mg tablets bid

1. Sontag S, Robinson M, McCallum RW, et al: Ranitidine therapy for gastroesophageal reflux disease: Results of a large double-blind trial. *Arch Intern Med* 1987;147:1485-1491

Please see next page for Brief Summary of Prescribing Information.

Glaxo/ ROCHE

ZANTAC® 150 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

May 1988

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Research Triangle Park, NC 27709

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CONTINUING MEDICAL EDUCATION

(Continued from Page 278)

RADIOLOGY

September 16-18—**Three-Day Seminar in Magnetic Resonance Imaging With Interpretive Workshops.** Los Angeles Radiological Society at Registry Hotel, Universal City. Fri-Sun. 18 hrs. $300. Contact: LARS, PO Box 91215, Los Angeles 90009-1215. (213) 827-9078.

October 31-November 4—**13th Annual San Diego Postgraduate Radiology Course.** San Diego Radiology Research and Education Foundation at Hotel del Coronado, San Diego. Mon-Fri. 27 hrs. $450. Contact: Dawne Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

October 31-November 1—**San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronada, San Diego. Mon-Tues. 28 hrs. $450. Contact: UCSD.

November 4-6—**8th Annual Interventional Course.** San Diego Radiology Research and Education Foundation at Hotel del Coronado, San Diego. Fri-Sun. 18 hrs. $350. Contact: Dawn Ryals, Ryals & Associates, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

December 9-11—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: Dawne Ryals, PO Box 920113, Norcross, GA 30092-0113. (404) 641-9773.

January 13-15—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Laguna Niguel. Fri-Sun. 18 hrs. $395. Contact: R. Dawne Ryals, PO Box 920113, Norcross 30092-0113. (404) 641-9773.

January 19-21—**Duplex Imaging.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Thurs-Sat. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 21-22—**Workshop on Percutaneous Disectomy.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Sat-Sun. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

January 24-27—**MRI for Technologists—Symposium and Workshops.** San Diego Radiology Research and Education Foundation at San Diego Marriott Hotel and Marina. Tues-Fri. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

February 23-25—**Advanced Seminars in Diagnostic Imaging.** San Diego Radiology Research and Education Foundation at Ritz-Carlton Hotel, Rancho Mirage. Thurs-Sat. Contact: Dawn Ryals, Ryals & Associates. (404) 641-9773.

SURGERY

September 16—**Ultrasonic Liver Surgery.** UCD at Hyatt Regency Hotel, Sacramento. Fri. 8 hrs. Contact: UCD.

September 17—**Los Angeles Society for Plastic Surgeons: 10th Annual Symposium.** Los Angeles Society of Plastic Surgeons. Sat. Contact: Joanne Cummings, c/o Dr Harold Rosenfield, 3600 Lomita Blvd, Torrance 90505. (213) 539-6500.

September 17—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

October 3-7—**6th Annual Comprehensive Review of Vascular Surgery.** UCLA Miramar Sheraton, Santa Monica. Mon-Fri. 32 hrs. $595. Contact: UCLA.

October 12-14—**Hip and Knee Reconstructive Surgery 1988.** UCLA at Sheraton Princeville Hotel, Kauai, Hawaii. Wed-Fri. Contact: UCLA.

(Continued on Page 284)

Applications Invited for Board Certification

A time limited **grandfathering** is presently in effect until December 1991. Three levels of certification are available: "Diplomate," "Fellow," and "Clinical Associate," depending upon amount and type of education and work experience in fields related to pain management.

Physicians, dentists, psychologists, and other health care providers who have been granted a doctorate from an accredited university and who have two years of approved clinical experience may apply for the **Diplomate Credential.**

Individuals trained at the Masters level in related health care disciplines with two years of approved experience may apply for the **Fellow Credential.**

Individuals with a Baccalaureate Degree or its equivalent and five years of experience may apply for the **Clinical Associate Credential.** All applicants must have significant work experience in pain management.

During the grandfathering period, educational degrees earned from accredited training programs and relevant professional work experience will be considered. The Board will review applications on an individual case basis for appropriateness. Certification is dependent upon adherence to the ethical standards of the Academy. Certified providers must demonstrate ongoing professional development.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 283)

October 29-30—**1988 Regional Review Courses in Hand Surgery.** American Society for Surgery of the Hand at Los Angeles. Sat-Sun. 12 hrs. $200. Contact: ASSH, 3025 S Parker Rd, Ste 65, Aurora, CO 80014. (303) 755-4588.

December 1-4—**Bone Grafting: Biology and Application for Maxillofacial Indications.** Plastic Surgery Research Foundation at Le Meridien Hotel Coronado Bay, San Diego. Thurs-Sun. 21 hrs. $350. Contact: PSRF, PO Box 33387, San Diego 92103. (619) 692-9115.

December 3—**Reider Laser YAG & Argon Laser/Brachytherapy Symposium.** Center for Health Education, Long Beach. Sat. 9 hrs. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

December 3—**Summary of Clinical Use of Argon, YAG and CO2 Lasers for Cutaneous Lesions.** Palo Alto Medical Foundation at Palo Alto Medical Clinic. Sat. 6 hrs. Contact: Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto 94301. (415) 321-4121.

December 3—**Cleft Palate Symposium.** UCD at Hyatt Regency Hotel, Sacramento. Sat. Contact: UCD.

January 13-14—**11th Annual Postgraduate Course: What's New in General Surgery.** UCD at Red Lion Motor Inn, Sacramento. Fri-Sat. Contact: UCD.

March 9-11—**Knee Reconstruction Surgery: ACL Repair, Patella Alignment and Total Knee Replacement.** Scripps Clinic and Research Foundation at La Jolla Marriott Hotel. Thurs-Sat. 30 hrs. Contact: Bonny Mower, Conference Coordinator, Department of Academic Affairs, Box 400S, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

March 16-19—**Surgical Forum.** Society of Graduate Surgeons at Beverly Hilton, Beverly Hills. Thurs-Sun. Contact: Director of Medical Education, Society of Graduate Surgeons, 5820 Wilshire Blvd, Ste 500, Los Angeles 90036. (213) 937-5514.

OF INTEREST TO ALL PHYSICIANS

September 15-18—**Decentralized Care of People With AIDS: An Educational Seminar for Developmental Approach.** Sonoma County Academic Foundation for Excellence at Flamingo Hotel, Santa Rosa. Thurs-Sun. $275. Contact: Mary Ellen Buechter, SCAFE, 3325 Chanate Rd, Santa Rosa, 95404. (707) 527-4121.

September 16-17—**AIDS and the Oncologist.** UCSF at Hotel Nikko, San Francisco. 13 hrs. $225. Contact: UCSF.

September 16-17—**AIDS: A Practical Program Designed for Community Based Physicians.** UCD at Hyatt Regency Hotel, Sacramento. Fri-Sat. Contact: UCD.

September 17—**Seminar on Caring for AIDS Patients.** UCLA at Century Plaza Hotel, Century City. Sat. Contact: UCLA.

September 17—**Treatment Issues With Adult Children of Alcoholics and Co-Alcoholics in Group and Individual Therapy.** Institute for Addiction Studies at Health Education Center, Oakland. Sat. $55. Contact: Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave, Oakland 94609-3081. (415) 652-7000.

September 23-25—**The Medical Office Laboratory: A Technological Revolution in Primary Care.** SDSU at San Diego Princess Resort. Fri-Sun. 18 hrs. Contact: SDSU.

September 24—**Lumbar Spine Disease: A Practical Approach for the Primary Care Practitioner.** Scripps Clinic and Research Foundation at Amphitheater, La Jolla. Sat. 5 hrs. $50. Contact: Bonny A. Mower, Dept of Academic Affairs, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

September 28-30—**Primary Care Medicine: Principles and Practice.** UCSF at the Portman Hotel, San Francisco. Wed-Fri. $365. Contact: UCSF.

(Continued on Page 364)

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INDICATIONS AND USAGE: This drug product has been conditionally approved by the FDA for the prevention and treatment of angina pectoris due to coronary artery disease. The conditional approval reflects a determination that the drug may be marketed while further investigation of its effectiveness is undertaken. A final evaluation of the effectiveness of the product will be announced by the FDA.

CONTRAINDICATIONS: Intolerance of organic nitrate drugs, marked anemia.

WARNINGS: The NITRO-DUR system should be used under careful clinical and/or hemodynamic monitoring in patients with acute myocardial infarction or congestive heart failure.

In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks in order to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

PRECAUTIONS: Symptoms of hypotension, such as faintness, weakness or dizziness, particularly orthostatic hypotension, may be due to overdosage. If during the course of treatment these symptoms occur, the dosage should be reduced or use of the product discontinued.

NITRO-DUR is not intended for use in the treatment of acute anginal attacks. For this purpose, occasional use of sublingual nitroglycerin may be necessary.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with NITRO-DUR. It is also not known whether nitroglycerin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Nitroglycerin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether nitroglycerin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NITRO-DUR is administered to a nursing woman.

ADVERSE REACTIONS: Transient headache is the most common side effect, especially when higher doses of the drug are administered. Headaches should be treated with mild analgesics while continuing NITRO-DUR therapy. If headache persists, the NITRO-DUR dosage should be reduced or use of the product discontinued.

Adverse reactions reported less frequently include hypotension, increased heart rate, faintness, flushing, dizziness, nausea, vomiting, and dermatitis. Except for dermatitis, these symptoms are attributed to the pharmacologic effects of nitroglycerin. However, they may be symptoms of overdosage. When they persist, the NITRO-DUR dosage should be reduced or use of the product discontinued.

CAUTION: Federal law prohibits dispensing without prescription. EDP #1030160
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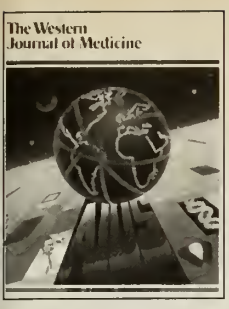
SPECIAL ISSUES



AIDS—A Global Perspective

The short and remarkable history of AIDS epidemiology began in 1981 with the description of the clinical syndrome in California and New York. In the 6 years that have followed, intensive epidemiologic studies have defined the mode of spread of AIDS and laid the foundation for current control efforts. Serosurveys and retrospective clinical studies have been used to trace the temporal origins of the pandemic prior to 1981, while prospective studies and an increasingly comprehensive worldwide surveillance system have provided more accurate data for the years following 1981. AIDS cases have now been reported and investigated throughout the world.

This issue, from the Special Programme on AIDS of the World Health Organization, considers the methods and limitations of AIDS case reporting and HIV serologic studies, summarizes modes of HIV transmission, defines geographic patterns of spread, and examines the epidemiology of HIV infections by continent.

—Jonathan M. Mann, MD
Director,
Special Programme on AIDS
World Health Organization,
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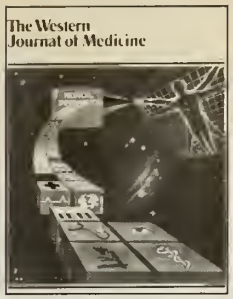

Medical Informatics

I would suggest that the computer in its relation to medicine is analogous to that of the microscope in the last century. . . . The analogous role that I believe the computer is now taking on is also that of a breakthrough tool—one enabling us to explore and better understand the informational and cognitive foundations of medicine. Its application to the classification and retrieval of data and to the management of information will result in a deeper insight into the structure of medical information and knowledge itself.

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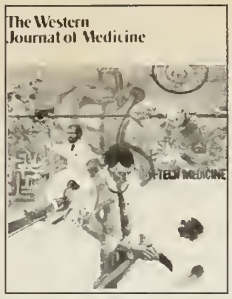

High-Tech Medicine

Progress in medical science seems to come in rushes. There are long periods of time during which we mainly fine-tune the status quo: third-generation drugs, better optics for endoscopes, more accurate assays, rapid development of x-ray film and so forth. Then, out of nowhere, a surge of new discoveries whose potential applications to medical practice seem limitless takes our breath away. We are now in such an epoch. Powerful and precise lasers. Almost unbelievable organ transplantation. Complex and uniquely informative magnetic resonance imaging and positron emission tomography. Exquisitely specific monoclonal antibodies. And the immense potential of modern molecular biology. This rush of new advances, collapsed into such a brief period of time, boggles the mind.

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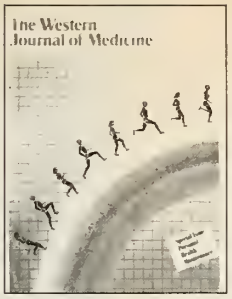

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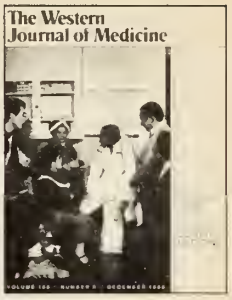

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—Malcolm S.M. Watts, MD

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Contraindications: *Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.*
Warnings: ***Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.*** *If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake.* ***Associated widened QRS complex or arrhythmia requires prompt additional therapy.*** *Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.*
Precautions: *The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of triamterene and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Angiotensin-converting enzyme (ACE) inhibitors can elevate serum potassium; use with caution with 'Dyazide'. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin[ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function. Thiazides may add to or potentiate the action of other antihypertensive drugs. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.*
Adverse Reactions: *Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions, nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.*
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JOURNAL OF THE ARIZONA MEDICAL ASSOCIATION

ARIZONA MEDICINE

SEPTEMBER 1988, VOL. XLV, NO. 9

Evolution of Therapeutics "Mother Nature Knows Best"

Marshall B. Block, M.D.

In contrast to the changes which my good parents, Beatrice and Charles, have observed in their lifetime (the change from horse-drawn wagons to automobiles and trains, planes to spacecraft, and radio to television), the last 25 years in medicine have appeared to be rather tame. However, we are now entering the "twilight zone" in our armamentarium to combat illness.

The treatment of hypertension, for instance, has evolved from the use of Reserpine and thiazides to "ACE" inhibitors and, shortly, atrial naturetic hormone. Controlling blood sugar levels with insulin hasn't changed, but changes in the type of insulin (biosynthetic Human) and routes of administration (nasal, intraperitoneal) have occurred which will have long range consequences. The treatment of peptic ulcer diseases has progressed from antacids (milk-alkali syndrome) to non-calcium antacids and H2 inhibitors. In the future we will probably be using somatostatin analogues (biosynthetically produced) to suppress parietal cell secretion. The cause of cancer, although still not clarified, has resulted in a great deal of knowledge about cell dynamics and our treatment has evolved from nonselective immunosuppressive toxic drugs to the use of compounds like Interferon and Somatostatin. Atherosclerotic cardiovascular disease therapy has evolved from digitalis leaf to prevention by lowering LDL and raising HDL levels and inhibiting cholesterol biosynthesis using drugs like Lovostatin. Clot lysing agents (TPA biosynthetically pro-duced) is now making its impact felt.

It is obvious that slow, but steady, progress in the unraveling of the pathogenesis of various disease states has resulted in more specific and powerful *natural* therapies. We have moved from nonselective shotgun *drug* usage to more specific rational approaches. Thus, the more we learn about "Mother Nature" the more we recognize the simplicity and specificity of control mechanisms. This is resulting in a revolution in our approach to therapeutics.

Within our lifetime, under our noses, there is the potential for medicine to uncover the genetic basis of cell regulation which has, and will continue to have, unforeseen consequences on our current therapies. We are truly in the "Golden Age" of medicine. The changes which my parents saw in their lifetime will be more than balanced by the revelations which we will see within the next ten years in medicine. ❑

Marshall B. Block, M.D.
Editor

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In This Issue

- Attorney General's Antitrust Suit
- Contemporary Academic Health Sciences
- New Members
- Malpractice -- Guest Editorial
- Letter to the Editor
- Classifieds

The Attorney General's Antitrust Suit

The American Tort Reform Association continues its education effort to help differentiate between the rhetoric and the reality of the Attorney General's lawsuit, which is being used to stall tort reform. The following is a report authorized by Orin Kramer, formerly Vice Chairman and Executive Director of Governor Cuomo's Advisory Commission on Liability Insurance, which is being mailed to all state legislators. The paper discusses the conspiracy theory and the evidence disputing it and then lays out the real driving forces behind the liability crisis.

Earlier in 1988 nine state attorneys general *(Alabama, Arizona, California, Massachusetts, Minnesota, New York, Texas, West Virginia and Wisconsin)* filed lawsuits charging antitrust violations in connection with the 1984-1986 liability insurance crisis. The defendants have denied any impropriety and disputed both the facts and the legal theories underpinning the litigation. Scholars of antitrust law have noted the absence of the traditional requisites of a successful antitrust action, and have suggested that the plaintiffs face a low probability of success. The purpose of this letter, however, is not to assess the merits of the litigation, which can only be resolved by the courts. Rather, the purpose is to address the public policy and political implications of the litigation, and in particular, the implications for public debate over the tort law system.

From a strictly legal perspective, the lawsuits charge the 31 defendants, including four major domestic insurance companies, with having colluded to narrow the coverage of the standard commercial general liability policy, and with exercising their market power to prevent competitors from offering broader coverage. The plaintiffs allege that the purported conspiracy largely eliminated the availability of pollution liability coverage.

From a political perspective, however, the litigation has been used by the plaintiffs and their philosophical allies in the plaintiff's bar community to validate a set of critical propositions with respect to the liability crisis. Their central proposition is that an insurer conspiracy -- rather than rising costs and unpredictability produced by developments in the tort law system -- was the primary cause of the recent liability crisis. Consequently, they conclude that legislators should leave the tort system alone, and should focus on restructuring the insurance industry's regulatory framework.

There is reason to suspect that the conspiracy theory can be more accurately viewed as a tactical foray in the battle against tort reform than as a serious causal explanation for the liability crisis. As noted below, the conspiracy theory has been uniformly rejected by academics and various governmental bodies that have examined the issue. Coincidentally or not, the attorneys general who led the investigation culminating in these lawsuits have been among the most vocal leaders of the anti-tort reform movement. While the lawsuits themselves carefully avoided alleging that insurer conspiracy caused the liability crisis, in press conferences scheduled around the country the plaintiffs -- and their trial bar supporters -- enthusiastically espoused the broad conspiracy theory. Presumably, the intended effect of their highly visible effort was to reframe the tort reform debate, to make the insurance

Continued on Page 6

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The Contemporary Academic Health Sciences

Today's academic health sciences libraries are faced with a variety of serious issues. The proliferation of medical literature and other health-related information sources, increasing prices for library materials (books, journals, etc.), budget constraints, educational demands, and rapidly changing technological developments are having an enormous impact on library operations and services. As a result, academic medical libraries and their parent institutions are reexamining their traditional way of doing things, and new and exciting ideas are emerging that will forever change the academic medical library as we know it today.

A special publication entitled *Challenge to Action; planning and evaluation guidelines for academic health sciences lib-raries* was issued in 1987 by the Joint Task Force of the Association of Academic Health Sciences Library Directors and the Medical Library Association. This report emphasizes the importance of coordinating institution-wide planning and development efforts in the area of information management in order to maximize economy and effectiveness. It encourages the library's active role in these planning procedures and suggests ways in which the library's information management resources and skills can contribute to the institution's activities in research, education and patient care. The report also urges the institution to provide continuing technological support (systems development) to strengthen the library's capabilities as an academic information services center. In general, *Challenge to Action* offers a framework for strategic planning and self-evaluation, and its guidelines offer library directors, and other policy makers in academic medical centers, standards against which to measure their own library and information services.

The University of Arizona Health Sciences Center Library is typical of the modern academic medical library and it too faces many of the issues mentioned above. Fortunately the AHSC Library's institutional support has always been strong and the Library is therefore better prepared than many of its counterparts to implement the recommendations of *Challenge to Action.* Last year, the Library installed the LS/2000 automated library system replacing the manual card catalog and offering online access to the Library's cataloged records (book, journal, and media titles) via public terminals set up for that purpose. Dial-up access to the system from labs, offices, and other remote location, including off-campus sites, is planned for implementation in 1989. The library has also acquired the National Library of Medicine's *MEDLINE* system on compact disk (CD-ROM) allowing direct user access to the *MEDLINE* database from microcomputer stations. A University-wide telecommunications system is in the process of development, and it will facilitate information linkages throughout the Arizona Health Sciences Center--including the Library. For example, campus access to LS/2000 will utilize this new system. Integrated Academic Information Management Systems (IAIMS) was the subject of one of the College of Medicine's Dean's Education Rounds presented in April 1987. The concept behind IAIMS is to gather, organize, and communicate, via computer linkages, various biomedical information components so they are received in a timely manner at the place where they are required--for example, in the physician's office, at the nurses' station, or at the patient's bedside. This information can come from many sources and be in various formats including patient records, laboratory test results, radiography reports, information from library books and journals, databases which include diagnostic information or treatment protocols. IAIMS will have a special impact on the future of information transfer, and the LS/2000 system now operational in the AHSC Library will be a major component of any IAIMS development in the Arizona Health Sciences Center.

The academic medical library remains one of the most valuable resources for any academic institution. It is the conduit by which most health-related information is channeled to academicians and their practicing colleagues. That role will not change for the library, but the methods of channeling information will be constantly changing and improving with each technological advance. The implications for improved health care are positive and exciting.

Thomas D. Higdon
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Arizona Health Sciences Center Library

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Continued from Page 2

industry rather than the tort law system the issue, and to impose upon tort reform advocates the difficult burden of disproving a conspiracy. Of course, the appeal of the conspiracy theory is that nobody can ever prove to a certainty that two or more parties did not collude someplace, somewhere, about something.

Whether or not that analysis is accurate, the recent litigation has reintroduced what had been discredited conspiracy theories into the public dialogue. To the extent such theories are viewed as credible, efforts to look seriously at difficult issues raised by the modern evolution of the tort law system will inevitably be set back. This letter offers some observations on the resurrected conspiracy theories and summarizes recent evidence on the behavior of the tort law system and its impact on the insurance mechanism. Addressing the thorny issues raised by the tort law revolution will not be easy under the best of circumstances, but the difficulty of that task will only be compounded if unsupportable conspiracy theories are allowed to distort the public debate.

I. Conspiracy Theory and the Evidence

The conspiracy theory has not suffered from a lack of examination. The theory has been analyzed by numerous academics, by a variety of independent state commissions, and by the Antitrust Division of the United States Department of Justice. The theory has been consistently characterized by those experts as inconsistent with generally accepted economic theory, unsupported by the evidence, and totally inadequate as an explanation of the crisis.

Indeed, the insurer conspiracy thesis is incompatible with everything mainstream economists believe about the structural conditions necessary to foster industry collusion. There is general agreement among antitrust scholars as to the conditions that are requisite to effective collusion.

First, economists agree that effective collusion requires a cartel-like industry structure: that is, a relatively small number of firms, and substantial market share concentration among the largest firms. By contrast, the property and casualty insurance industry has over 3500 companies, and even the largest has less than 10% of total market share.

Second, collusion requires an industry with high entry barriers so that new competitors cannot come in and undercut the cartel. The property and casualty insurance industry has notoriously low entry barriers, indeed, those low entry barriers were a major cause of the destabilizing price competition that the industry experienced in the early 1980s.

Finally, the purpose of collusion is profit maximization. Collusion to raise prices and then to refuse to sell the product at all over an extended period of time makes no economic sense; it yields no profit. In the entire history of antitrust law, there are few examples of cartels colluding to deny customers access to their products.

Beyond the lessons of economics, even if the facts alleged by the attorneys general were true -- which the defendants have emphatically denied -- the charge that insurer conspiracy caused the liability crisis is incompatible with the actual facts of the crisis.

The recent liability crisis had two basic characteristics: insurance rates rose sharply for many insureds, and some insureds were unable to find coverage at any price. The essence of the litigation is that the defendants colluded to produce restrictive policy forms. There are no allegations in the lawsuits relating to collusive pricing. Regardless of how those policy forms were developed, there is no way those forms can explain what amounted to a crisis of affordability and availability.

In fact, it is difficult to establish any linkage between the new policy forms and the crisis. While the new form was not approved in most states until 1986, the crisis began in 1984. While the crisis affected every state, six states -- including several now involved in the litigation -- never approved key provisions of the form for general use. Most fundamentally, the new policy forms have played a limited role in the insurance marketplace. Claims-made policies have never constituted more than 10% of the total general liability market in any given year. In other words, assuming there were a plot to substitute this new policy form for the pre-existing (and still existing) occurrence policy form, the "plot" clearly failed. A plot that failed could not have caused the crisis.

II. Driving Forces Behind the Liability Crisis

In part, independent experts have rejected the various conspiracy theories because of the weaknesses and contradictions implicit in those theories. But in large part, they have done so in response to compelling evidence as to the real causes of the liability crisis.

A. The Tort Law Revolution

In response to the liability crisis, many states either established independent commissions or undertook special studies to examine the root causes of the crisis. The findings of those studies generally mirrored the conclusions reached by most independent academics: that the central driving force behind rising liability rates has been the surge in costs produced by the tort system. Many experts found that the effects of the tort cost surge were exacerbated by the insurance industry's historic cyclicality, which is discussed in a separate section below.

The impetus behind the attention focused on the tort system was, of course, the liability crisis. Historically, public interest in tort law has ebbed and flowed in response to periodic crisis in insurance markets. Today, conditions in those markets continue to improve; insurance coverage has returned for most activities, and the period widespread, sharp rate hikes is now history. The risk today is that as the crisis that fueled the recent debate recedes, so will public interest in the workings of the tort law system.

In reality, the recent behavior of the tort system raises issues of profound importance -- issues that would warrant public attention even if there were no such thing as

liability insurance. In 1985, it is estimated that tort litigation expenditures nationwide totalled between $29 billion and $36 billion. To put those figures in perspective, in 1987 total budget authority for the federal Departments of State, Housing and Urban Development, Justice, Commerce and Interior combined totalled under $30 billion. The aggregate budgets of the Department of Education and Transportation totalled $31 billion.

Agency expenditures -- on the state or federal level -- are the product of an extended process of legislative review. Whatever the limitations of appropriation processes, they afford legislators the opportunity to establish spending priorities, to gather input from the relevant constituencies, and to assess the costs and benefits of spending decisions from a broad societal perspective. It would be inconceivable if the field officers in agencies were given unlimited discretion to make their own spending decisions, with no expenditure ceilings and without the discipline of a centralized planning process.

Yet because of the institutional structure of our judicial system, the billions of dollars moving through the tort system each year are dispensed precisely that way. A decentralized system for distributing billions of dollars in tort expenditures is not necessarily a bad thing, but society has a powerful interest in understanding how those dollars are being spent, and what the distributional and broader societal implications of those spending decisions might be. Whatever one's philosophical disposition toward the tort system, its expenditures clearly have important societal implications -- in terms of the cost and availability of goods and services, the propensity to innovate, and our international competitive position. In short, the workings of the tort system should be more than just a cyclical political issue, the saliency of which varies with the phases of the insurance business cycle. Public policy toward the tort system should be an ongoing item on the nation's policy agenda. The greatest threat posed by the resurgent conspiracy theory is not that it will someday be affirmed by economists or judges, but that it will help push tort law policy issues to the back burner.

Indeed, despite the improvement in insurance markets, developments in the tort law system continue to have an invidious effect on the insurance mechanism. On an inflation-adjusted basis, insurance rates are higher today than a decade ago. At any given point in time, factors unrelated to tort law (e.g., the phases of the insurance cycle) may impose upward or downward pressure on insurance rates. But over time, insurance rates will reflect the underlying cost of settling claims. If the underlying surge in claim costs addressed below is not addressed, over time insurance rates will continue to rise for insureds and direct claim costs will continue to rise for self-insureds, even on an inflation-adjusted basis. And for those activities where the evolution of tort law remains erratic and unpredictable, crises of insurance unavailability will periodically recur. From a political perspective, the recent insurance crisis may have disappeared, but the failure to control claim cost growth simply assumes a continuing squeeze on insurance consumers.

The sections below recap the key evidence on the evolution of the tort system. Two trends stand out. First, over the past decade there has been a surge in personal injury award levels, which has meant higher claim costs for insurers and self-insureds, and higher rates for insurance consumers. Second, there has been an unpredictable expansion of concepts of tort liability, which has reduced the range of risks deemed "insurable" and exacerbated pressures for higher rates.

1. Tort Awards

For the neutral observer, the debate over the quantitative evidence is often difficult to follow, because each side has its own statistical "evidence" that is irreconcilable with the "evidence" presented by the other side. Hence, it may be useful to review the evidence raised by those who deny the existence of a litigation crisis.

There are two issues: the frequency, or rate, of litigation, and the cost of that litigation. Since the defenders of the current tort system tend to focus on the rate of litigation and tend to ignore the cost data, we should begin with the frequency issue. Those who say there is no lawsuit crisis like to point out that from 1975 to 1984, total federal civil litigation rose by only 123%, which they suggest is hardly an explosion. What they ignore is that that growth was 13 times faster than the growth in the U.S. population over the same period.

Those critics also like to cite state court data showing that from 1978 to 1984, filings rose 9% while population grew 5% -- hardly an explosive differential.

What they ignore is that the so-called state court data is only a 13-state sample, and in only two of those states are the data complete. Thus in California, for example, the "sample" showed an increase of only 12%, whereas in reality filings rose 55% if municipal court actions are included.

The real problem with the critics' argument, though, has nothing to do with its statistical deficiencies, it's that the critics are flogging a straw man. There have been substantial rises in overall civil litigation and in overall tort litigation, but those increases are arguably manageable and are not the source of the crisis. From the perspective of litigation frequency, the problem is the explosion in certain kinds of tort litigation.

The majority of tort actions are automobile accident cases, and thus overall tort litigation rates tend to reflect trends in the incidence of automobile accident litigation. Because of lower speeding limits and no-fault auto systems, automobile accident litigation rose only as fast as the U.S. Population over the 1981-1984 period. But non-auto torts rose ten times as fast as the population over that period. As an example of what has been happening outside the automobile litigation area, from 1974 through 1985 federal product liability litigation alone rose by 758% -- 63 times the rate of population growth.

If the critics are addressing the wrong problem when they talk about litigation rates, they ignore the data on the cost of litigation entirely. From society's perspective, what matters is not so much the frequency of litigation but the costs of the awards produced by that litigation. Throughout the lawsuit crisis debate, nobody has offered any significant evidence suggesting that there has not been an explosion in award levels.

The most comprehensive and respected work on litigation costs comes from the Institute for Civil Justice (ICJ), an independent subsidiary of the Rand Corporation. Most of their analysis focuses on San Francisco County and Cook County, Illinois, where there is particularly good historical data.

After adjusting for inflation, average award levels rose from $57,000 to $252,000 in Cook County, and from $74,000 to $302,000 in San Francisco between 1960-1964 and 1980-1984 periods. The total number of dollars awarded also rose sharply over the same period, quintupling in Cook County and doubling in San Francisco.

ICJ has also compiled specific data for product liability and medical malpractice. After adjusting for inflation, the average product liability award rose from $308,000 to $1,105,000 in San Francisco between 1975--1979 and 1980-1984. In medical malpractice, the increase in San Francisco over the same period was from $644,000 to $1,162,000.

Some proponents of the view that the tort system is essentially sound attach great importance to the fact that median (the halfway point on a scale or 50th percentile) award figures have not been on a clear uptrend, rising slightly in some jurisdictions while remaining static or falling in others. Average awards (the sum of all awards divided by the number of awards), on the other hand, have been rising exponentially. The argument is that medians represent "typical" cases, award levels for "typical" cases have not been rising dramatically, and thus there is no problem.

The argument ignores the fact that to those who must pay those awards -- whether a self-insured city or an insurer -- what matters is the total costs of paying awards, not the distribution of those costs between "typical" and "atypical" cases. The cost surge has been driven not by any sharp increases in small, garden-variety lawsuits, but by a surge in the number and cost of cases involving serious injuries, or involving fields such as product liability and medical malpractice. Thus over the 1982-1984 period, in Cook County and San Francisco million dollar awards represented less than 5% of all verdicts but accounted for 68% of total award dollars.

The other key distinguishing characteristic of the awards that are driving up costs is that they are paid by deep-pocket defendants. Two-thirds of all defendants in tort actions are individuals, but the remaining third -- corporation, local governments, and non-profit organization -- pay out three-quarters of all award dollars. Theoretically, the explanation could be that deep-pocket defendants cause more serious injuries than do individual defendants. But there is substantial evidence that a deep-pocket defendant will pay more for a given injury than would an individual causing the same injury. The more serious the injury, the greater the discrepancy.

2. Insurance Claim Costs

For every lawsuit going to verdict, 50 lawsuits are settled. And for each case that is settled, countless more disputes are resolved through an insurance claim without resort to litigation. Consequently, the real cost paid by society is not measured by verdicts per se. Court awards matter primarily because of their multiplier effect on the cost of settling claims -- claims that are settled on the basis of how the parties believe the claims would be resolved if taken into litigation.

The insurance line that serves as the best prism for gauging the effects of the tort system is general liability. Between 1966 and 1986 general liability incurred losses rose 2664%, compared to a 238% rise in inflation, a 364% increase in medical care costs, and a 445% increase in gross national product. In 1984 and 1985 alone, general liability incurred losses grew by 24% and 54%, respectively.

While on a nationwide basis there has not ben a sharp increase in litigation rates (states such as California are exceptions to the rule), there has been a sharp cost rise in the automobile area. The reason is that while little has changed in settlement patterns for the common, low-damage fender bender, award levels and claim settlements have risen sharply for automobile accident cases involving serious injury. Consequently, over the 1977-1986 decade personal passenger auto liability incurred losses grew by 180%, placing upward pressure on auto insurance rates across the nation.

3. Self-Insureds

Those who argue that rising insurance rates reflect some defect in the insurance mechanism rather than the behavior of the tort system have difficulty rebutting the experience of self-insureds. Between 1978 and 1985, claim payments rose by 407% and 348% for New York City and Los Angeles, respectively. In Dallas, claim payments rose by 104% between 1982 and 1986 (pre-1982 data is unavailable). In fiscal year 1986-1987, Michigan paid out a record $45.5 million in court judgments and settlements, a 29% rise from the prior year.

4. Expansion of Liability Principles

Rising award levels and claim costs reflect two phenomena: increased valuations by judges and juries of the dollar value of serious injuries, and an expansion of the circumstances under which liability may be imposed on some defendant. Regardless of their ideological persuasion, independent observers are unanimous in the view that liability doctrines have been broadly expanded in recent years, and that that expansion has occurred in unpredictable ways.

The primary goal of traditional tort law was to reduce accident rates by deterring unreasonable risky con-

duct. By definition, unavoidable of unforeseeable accidents cannot be deterred. The goal was not to eliminate all risks or compensate all injuries, but to encourage socially and economically productive activity while discouraging unreasonably risky activity. Americans expected the law to be rooted in concepts of fairness, which meant that liability should be limited to instances where a defendant was at fault -- where some misconduct caused an injury.

Under the traditional fault-based regime, the plaintiff had to establish four things to recover:

- That the plaintiff was someone to whom the defendant had a duty to exercise reasonable care;
- That the defendant was at fault - that he had failed to exercise reasonable care.
- That the defendant's conduct was the proximate cause of the plaintiff's injury and
- That the plaintiff had suffered actual loss or harm.

Today, those historic principles are barely recognizable.

Traditionally, people had duties only to those with whom they came into direct contact. A professional -- say, an accountant --could only be sued by the person to whom he provided the professional service. Today if a prisoner commits suicide, the architect who designed the prison may be liable on the ground that the prison design made suicide too easy for prisoners. The fact that the architect had no direct relationship with the prisoner is now irrelevant. Defendants today re frequently found liable to people they never know existed.

Traditionally, the law expected us to exercise reasonable care to avoid injuring others. Reasonable care was the care a "reasonable person" -- a person of ordinary prudence -- would have used under the circumstances. Because the law wanted both parties to act carefully to avoid accidents, the plaintiff also had a duty of care. If the plaintiff's negligence contributed to his accident, under the rule of contributory negligence he would not recover.

Today in product liability cases, defendants are commonly held strictly liable; their degree of care can be legally irrelevant. If a product malfunctions, the fact that an occasional product defect might be unforeseeable or even technologically unavoidable does not matter.

Today, most states have abolished contributory negligence in favor of comparative negligence, whereby a plaintiff can recover even if the court finds he was primarily responsible for his own injury. The defendant's claim that its product represented the "state of the art," that the product met the highest know industry standards and satisfied all the regulatory tests no longer bars the plaintiff's recovery. Plaintiffs have recovered where the risk created by the defendant's conduct was not only unknown but was scientifically unknowable when the harm was done.

Under the common law, there were two requisites to establishing causation. First, specific conduct by the defendant must in fact have caused the injury. Second, the injury had to be a reasonable foreseeable consequence of that conduct. If the injury wasn't foreseeable, the defendant wasn't liable. Today the requirement that the plaintiff prove that the defendant's conduct caused the injury has been watered down. For example, in California, where a plaintiff can't establish which manufacturers' product caused an injury, under the theory of market share liability the plaintiff can recover the entire industry. In toxic tort cases, plaintiff's needn't necessarily prove that the defendant's product, or a chemical on the defendant's premises, caused the disease; he need only prove that the product or chemical has some statistical correlation with the disease and might have increased the probability of incurring the disease.

Traditionally, in personal injury cases actual physical injury was required to permit recovery. Damages were available for accompanying emotional injury, such as pain and suffering, but only once actual physical harm was established. Today a bystander witnessing an airplane crash can sue the airline for his emotional distress. And some jurisdictions permit recovery where the only injury is the fear that exposure to some product or substance might cause some real injury in the future. In effect, exposure to risk is now a compensable injury.

In the aggregate, those changes reflect a redefinition by the courts of the purposes of tort law. Whereas the traditional system aimed to deter dangerous conduct and punish those who engaged in such conduct, today's system aims at compensating the broadest forms of injury, independent of any finding of fault. Whatever one's views of the merits of running a compensation system through the courts, doing so wreaks havoc on the insurance mechanism. Insurance is a cost-spreading mechanism. Where the law is stable or evolves slowly and in reasonable predictable ways, insurers can project future claim costs and set rates accordingly. But when the law controlling an activity is constantly being expanded, future liability is unpredictable and therefore uninsurable. The new policy forms which are the local point of the antitrust litigation are a natural response by insurers seeking an economic basis on which to provide coverage in an increasingly, unpredictable legal environment.

Most experts believe that the industry's historic cyclicality exacerbated the impact of rising tort costs and contributed to the severity of the recent crisis. Insurance firms have two sources of income: investment income (income from investing their assets, including premium revenues not yet paid out in claims) and underwriting income (basically, the difference between premiums and underwriting costs, including claim costs). In the early 1980s, record high interest rates induced insurers to bid aggressively for premium dollars that could produce high investment returns. The severe price competition produced declining rates for insureds and growing underwriting deficits for insurers. Over the short-term, those underwriting deficits were covered by rising investment income. But with the unexpected onset of disinflation and a period of lower interest rates, the growth in investment income slowed, the "investment subsidy" covering severe underwriting losses disappeared, and the underwriting deficit --

which had been inflated by the tort cost surge -- had to be addressed. In effect, high interest rates and strong investment income had hidden the surge in claim costs. When rates were readjusted to reflect the cost of settling claims, insureds felt the full effect of that surge.

The industry's cyclicality created inadequate pricing in the early 1980s, which in turn contributed to the suddenness of the 1984-1986 price hikes. But the level to which rates have risen in recent years reflects the cost pressure created by the tort system, not the industry's cyclicality.

III. Conclusion

Over the short term, there may be some political benefits in some quarters accruing to those who blame the liability crisis on insurer conspiracy. Undoubtedly, there are those who genuinely believe in the theory. For those committed to sustaining the tort law revolution, turning the spotlight on the insurance industry makes good tactical sense. And for those seeking repeal of the industry's historic antitrust status, the conspiracy theory serves as a necessary intellectual foundation.

Ultimately, however, certain laws of economics are immutable. Either we control the costs produced by the tort system and achieve some degree of predictability in the evolution of tort doctrine, or consumers will be forced to pay for steadily rising claim costs and face occasional bouts of insurance unavailability. Over the long term, I would suggest that the failure to address those realities will make for both bad public policy and bad politics.

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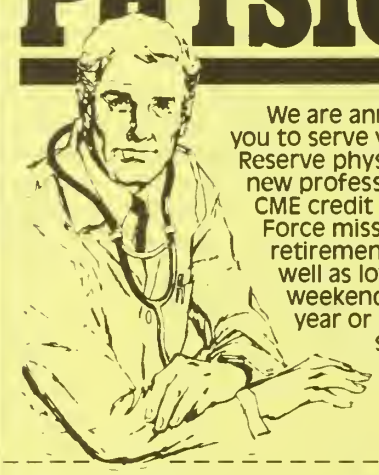

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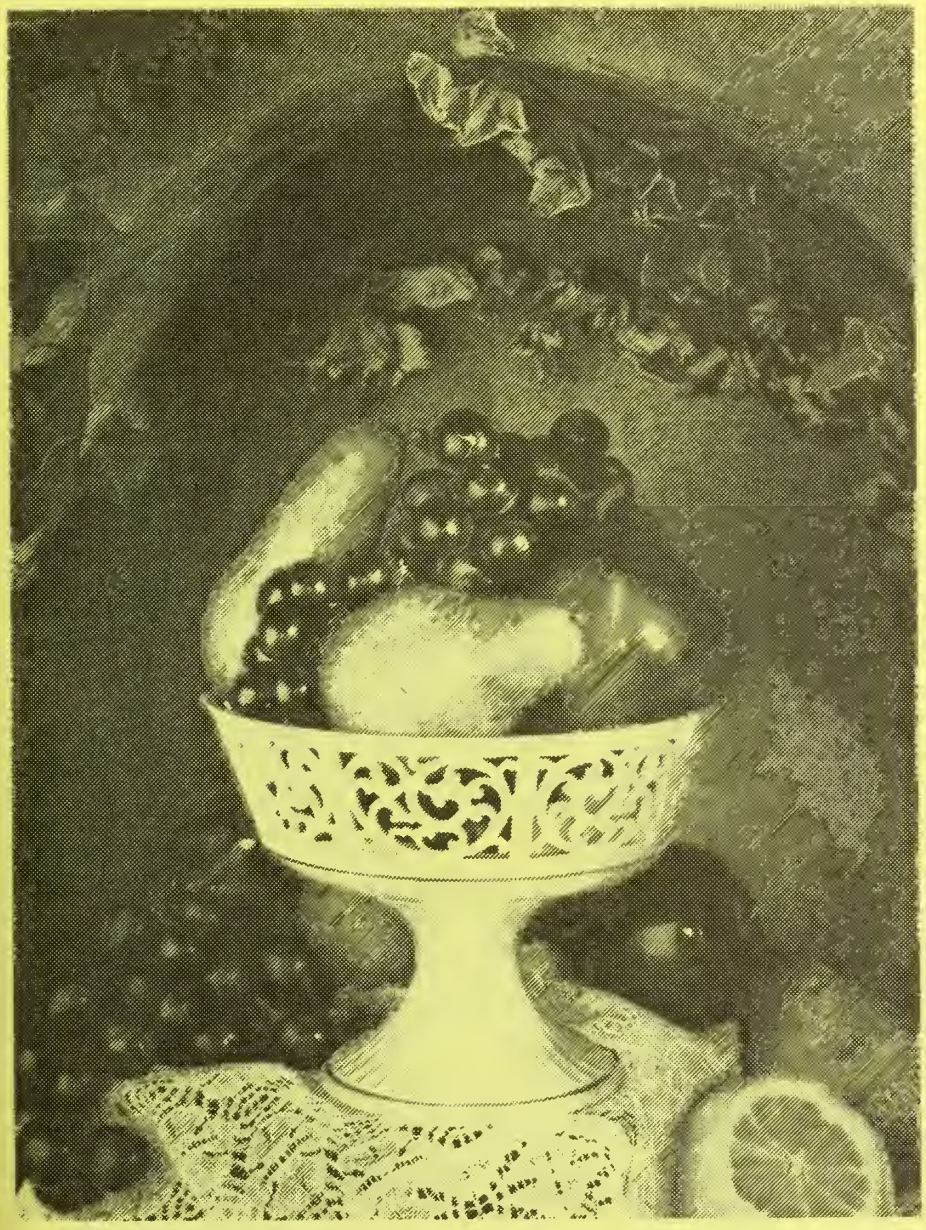

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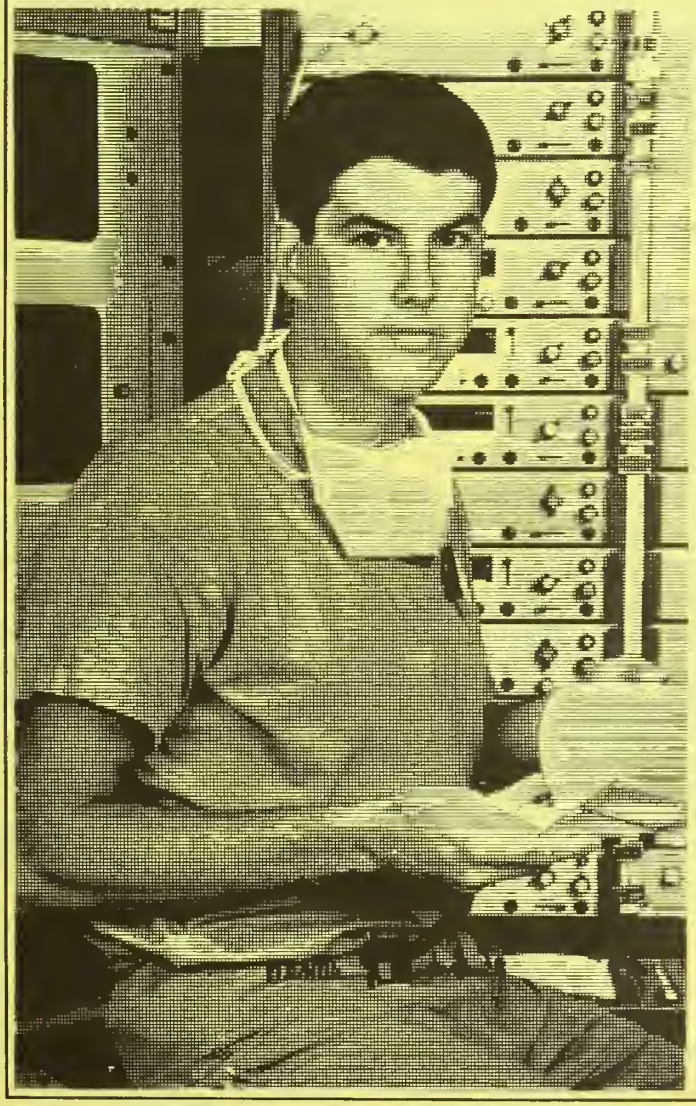

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Malpractice: A Poor Prognosis for Health in America

Guest Editorial

Throughout civilization the fall of every society has usually been heralded by the abandonment of the very principles, philosophic tenets and social institutions which led to its greatness.

In America today, we can trace three great principles which underlie the very foundation of our society. The first of these is the work ethic which is derived from the Calvinist 'doctrine of good works.' Next are rights to property as elaborated by John Locke. Simply stated, these are our rights to retain and enjoy that which is the fruit of our labor. The third principle is that of individualism and free enterprise as embodied in the doctrine of 'laissez-faire,' propounded by Adam Smith. All three of these principles are dear to the hearts of independent, free peoples everywhere.

However, these principles have been, in large part desecrated and ridiculed by politicians and lawyers. In particular, perversion of the concept of torts, as practiced by the legal profession in this country has made it possible for them to circumvent the work ethic and acquire property, not by labor, but by confiscation of the wealth of others.

Torts had their origin in primitive Anglo-Saxon tribal law, and were used in the days of the king as a means of guaranteeing civil justice to 'common people;' that is to say, people not of noble ancestry. Indeed, the intent of the tort was to 'make whole' those common people (people of ordinary ancestry) who had been damaged by other common people. Needless to say, the operative concept in tort law is the principle of negligence, or failure to take proper care.

This concept of 'the tort' has been abused and misapplied, so that it may be used without regard to the criterion of failure to take proper care. For instance, most physicians are painfully aware of the fact that patients may die, or suffer a poor outcome as a result of complications arising, not only out of treatment, but also out of the disease process itself. These complications rarely (less than 25% of the time) occur because the physician has failed to take proper care. Nevertheless, by abusing the concept of torts, often with the aid of questionable expert testimony, malpractice attorneys, and plaintiff, patients are able to confiscate large amounts of property while circumventing the work ethic and violating the principle of rights to property (John Locke).

This perversion of tort law, and its misapplication by the legal-judicial profession in America, has led to abandonment of the work ethic and the principle of 'rights to property' in favor of accumulation of wealth by confiscation of other peoples' property. Thus, stripped of any relationship to fault, the tort has, in effect, become a tool for compensating the victims of ill-fortune, and enriching their attorneys at the expense of the rest of society.

Today this activity portends destruction for not only the institution of medicine, but other institutions as well. All of these are threatened by this abusive application of torts and the resultant lack of affordable insurance which accrues from such misapplication.

Americans cannot hope to continue to enjoy the quality and availability of medical services to which they have become accustomed unless the profession and its practitioners are treated with more care and consideration. ❑

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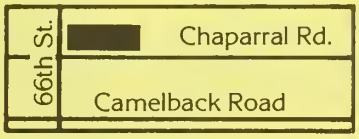

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LETTER TO THE EDITOR

In his editorial "Loss of Control" Arizona Medicine, May, 1988, Marshall Block draws an invalid analogy between his father's business becoming unionized, and the loss of autonomy that physicians are experiencing today.

A businessman seeks to maximize profits and minimize overhead costs. While unionization has certainly hampered the ability of some firms to compete, most have successfully transferred costs to the consumer, as price increases for the product.

The situation confronting physicians is entirely different. We are becoming de facto employees of government and private insurance companies, yet lack any typical employee benefits. The linkage of a medical license with acceptance of a dictated fee schedule reflects the complete absence of collective bargaining and removes our professional status. We are increasingly placed in the position of Dr. Block's father's employees, who recognized the need to organize as a counterbalance to management's whims.

It is often postured that as "dedicated" physicians, we are not entitled to the benefits and working conditions prevalent in our society. Usually the term "dedication" refers not to one's commitment to quality care, but rather constitutes a reproach by materially comfortable individuals who simply do not wish to pay for professional care. Society wants to pay a discount price for a flawless medical outcome while retaining the right to unlimited monetary damages for an adverse result. These expectations are on a collision course, with physicians right in the middle.

We are constantly chided to adapt to the changes in health care and societal attitudes. Yet, compared with other countries, the expectations of Americans are unrealistic. Chairman Lee Iacocca decries the high cost of medical care, insists on controls for physicians, and then draws a salary and benefit package of 28 million dollars for one year. This economy and society will show neither mercy nor respect toward a profession that will not stand up for itself. Our timidity will be rewarded with a professional burial.

Indeed, our society's desire for quality care, and "bright...compassionate individuals to continue to choose medicine" is currently inconsistent with an increasingly punitive and totalitarian approach toward physicians. This approach will inevitably reduce the quality of applicants to medical school. The reduction in applications to medical schools, coupled with the sixteen percent increase in applications to law schools, is in fact the harvest of societal values and attitudes, not the fault of current physician "counselling" of our youth. And the brain drain is just beginning.

Yet, for physicians currently in practice, the dramatic changes will provide opportunities for self-examination. As bright human beings, perhaps more aware than others of mortality, we may make more mid-course corrections in our careers than previously. As we experience more and more "employee counselling," we will perhaps learn from other workers and ultimately be forced to unionize, retire, or seek new life challenges, devoid of governmental sanctions.

Our perceptions will clarify when we consider that only value-for-value relationships are truly sustaining. The physician side of the relationship cannot be debased without an ultimate impact upon the society which is partner to the relationship. Patients' needs may not change, but they are provided differently throughout the world, for better or worse. In its zeal for cost cutting and controls, American society to date only sees a "win-win" situation with physicians. As physicians, we will hopefully resist becoming "molded," care for our current patients, and ponder future options. ✉

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Clinical Investigation

Humid Air Increases Airway Resistance in Asthmatic Subjects

MOIRA L. AITKEN, MB, MRCP; JOHN J. MARINI, MD; *and* BRUCE H. CULVER, MD, *Seattle*

This work was presented at the 50th Annual Meeting of the American College of Chest Physicians, October 1984, Dallas.

Eight persons with asthma were exposed to seven air conditions varying in temperature (37°C to 49°C [98.6°F to 120.2°F]) and water content (44 mg H_2O per liter to 79 mg H_2O per liter). Normocapnic hyperventilation for three minutes at 40% maximal voluntary ventilation was carried out for each condition. A constant-volume body plethysmograph measured the functional residual capacity and specific airway conductance (SG_{aw}), followed by two forced expiratory maneuvers. Measurements were taken before and 1, 5, 10, and 20 minutes after each challenge. Air conditions with 100% relative humidity caused a fall in the SG_{aw} that was maximal in 1 minute. Air conditions at 100% relative humidity caused a greater fall in both the forced expiratory volume in 1 second (FEV_1) ($P<.05$) and the SG_{aw} ($P<.005$) than did conditions of the same temperature but less water content. At 44°C and 100% relative humidity, the mean percent change in FEV_1 and SG_{aw} was −2% and −40%, respectively, at 1 minute after challenge. Of the conditions examined, the optimal temperature was 44°C, and we speculate that the optimal water content is less than 44 mg H_2O per liter. Inhaled water concentrations exceeding 44 mg H_2O per liter should probably not be used in patients with asthma.

(Aitken ML, Marini JJ, Culver BH: Humid air increases airway resistance in asthmatic subjects. West J Med 1988 Sep; 149:289-293)

Bronchoconstriction often occurs when persons with asthma exercise or do eucapnic hyperventilation when breathing cold air.[1-8] Usually little bronchoconstriction occurs when asthmatic subjects breathe air of 37°C (98.6°F), 100% relative humidity—44 mg H_2O per liter water content.[3] We previously showed that bronchoconstriction also occurs when persons with asthma hyperventilate while breathing heated air at 50°C (122°F), 100% relative humidity (83 mg H_2O per liter).[9]

Inhaling nebulized distilled water produces bronchospasm due to a hypo-osmolar challenge.[10] Because warm humid air would be expected to deposit water on the bronchial mucosa, we questioned whether the bronchospasm we had observed with breathing at 50°C, 100% relative humidity was induced by hypo-osmolality or by an additive effect of water and temperature. We therefore examined the airway response in asthmatic subjects to inhaling hot humid air of increasing temperature with a constant water content—selectively increasing heat delivery—and then increasing both temperature and water content, thereby increasing the heat delivery and water content simultaneously.

Methods

Subjects

We studied eight treated patients with asthma: six men, two women, aged 25.8 ± 7.3 years (mean ± standard deviation; range, 19 to 41 years). Baseline spirometry showed a forced expiratory volume in one second (FEV_1) of 3.2 ± 0.8 liters, range, 2.07 liters to 4.24 liters, percent of predicted, 87% ± 23%; a forced vital capacity (FVC) of 4.8 ± 1.1 liters, range, 3.18 liters to 6.00 liters; and a forced expiratory flow rate measured between 25% and 75% of the FVC ($FEF_{25-75\%}$) of 2.3 ± 1.7 liters per second, range, 1.26 liters per second to 3.24 liters per second. The FEV_1 was 66.6% ± 5.3% of the FVC. All gave informed consent for a protocol approved by the committee of the University of Washington School of Medicine for the Protection of Human Subjects. Each showed a significant response to 20 breaths of a nebulized, undiluted solution of 1% isoetharine[11] in one or more of these spirometric indices: FVC, FEV_1, or $FEF_{25-75\%}$. A questionnaire concerning medical history, current medications, smoking history, and exercise symptoms was administered. All subjects were nonsmokers and had had intermittent episodes of cough and wheeze for at least 15 years. All experienced exercise-induced asthma. The last exacerbation of disease was more than four months previously. Five subjects had been using a theophylline preparation, six an inhaled β-agonist, and one inhaled steroids.

Apparatus

A machine specifically designed to provide large quantities of air adjusted to the temperature and humidity condi-

From the Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Washington School of Medicine and the Pacific Medical Center, Seattle (Drs Aitken and Culver), and the Department of Respiratory Diseases, Vanderbilt University School of Medicine, Nashville, Tennessee (Dr Marini).

Supported in part by the National Institutes of Health grant No. 03630.

Reprint requests to Moira L. Aitken, MD, MRCP, Pacific Medical Center, 1200 12th Ave S, Room 10402, Seattle, WA 98144.

ABBREVIATIONS USED IN TEXT

$FEF_{25-75\%}$ = forced expiratory flow rate between 25% and 75% of total vital capacity
FEV_1 = forced expiratory volume in 1 second
FRC = functional residual capacity
FVC = forced vital capacity
MVV = maximal voluntary ventilation
SG_{aw} = specific airway conductance
ΔSG_{aw} = change in specific airway conductance

tions required was connected by a valved manifold to a constant-volume plethysmograph (Figure 1). This assembly allowed the specific airway conductance (SG_{aw}) and the functional residual capacity (FRC) to be determined within seconds of terminating each hyperventilation challenge. Details of design are provided in a previous communication.[9] Temperature and humidity of the inspirate were measured 10 cm upstream from the lips. Temperature was measured with a mercury thermometer. Humidity was measured using a hygromechanical strip sensor (model #8501 A, Hygrometrix Inc, Oakland, Calif). Carbon dioxide was added 150 cm upstream. Normocapnic hyperventilation of conditioned air was achieved using a modification of a method described previously.[9] During hyperventilation, the manifold was continuously evacuated at a predetermined rate by a controlled vacuum. A 13-liter spirometer joined to a side port of the expiratory line served as a reservoir to buffer transient deviations from the desired rate of ventilation. A variable resistor modulated by the spirometer bell provided the signal to a meter that cued a patient to the desired level of ventilation. The carbon dioxide tension of the exhaled air was sensed at the mouthpiece by the probe of a rapidly responding gas analyzer (LB-2, Beckman Instruments Inc, Schiller Park, Ill). During measurements of the SG_{aw} and the FRC, the plethysmograph was isolated from the conducting segments of the manifold by closing solenoid shutter valves at the points of entry and exit.

Protocol

Normocapnic hyperventilation trials were performed with each of the seven air conditions shown in Table 1 and

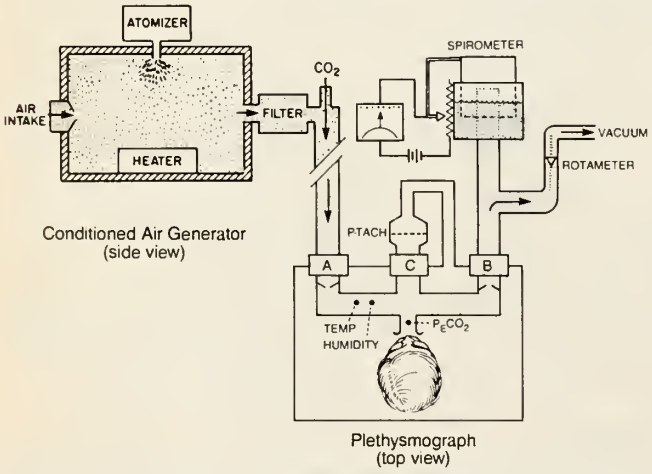

Figure 1.—The figure shows the testing apparatus used. During each hyperventilation trial, a one-way flow of conditioned air enters and exits the plethysmograph at a predetermined rate through heavily insulated tubing. By adjusting shutters A, B, and C, the plethysmograph can be made functional within seconds of discontinuing the challenge. P_ECO_2 = partial expiratory carbon dioxide tension, P-TACH = pneumotachygraph, TEMP = temperature

TABLE 1.—*Temperature and Humidity of 7 Air Conditions Used to Test Airway Response in Persons With Asthma*

Air Condition	Temperature, °C (°F)	Absolute Water Content, mg/liter^{-1}
1	37 (98.6)	44
2	40 (104.0)	44
3	44 (111.2)	44
4	49 (120.2)	44
5	40	52
6	44	63
7	49	79

Figure 2. A hyperventilation target of 40% of maximal voluntary ventilation (MVV) was used for each exposure. The MVV was estimated as 35 times the forced expiratory volume in one second, measured on the first day of the study. Testing was conducted over one to five days, depending on the response. If the specific airway conductance decreased more than 30% after challenge, no further testing was done that day. Because seven different air conditions were tested, all subjects had more than one challenge on some days.

The subjects were trained to pant appropriately for measurements made with the body plethysmograph.[12,13] Before each challenge, three to five baseline determinations of functional residual capacity and specific airway conductance were made and two forced expiratory spirometric maneuvers were done with the subjects breathing ambient air. Conditioned air was then drawn by vacuum through the manifold, and temperature and relative humidity allowed to stabilize to the specific condition under study. With nose clips placed, each person then hyperventilated normocapnically from the mouthpiece for three minutes. The partial pressure of carbon dioxide was maintained at the initial resting level by adding CO_2 to the inspirate. After completing the challenge, the

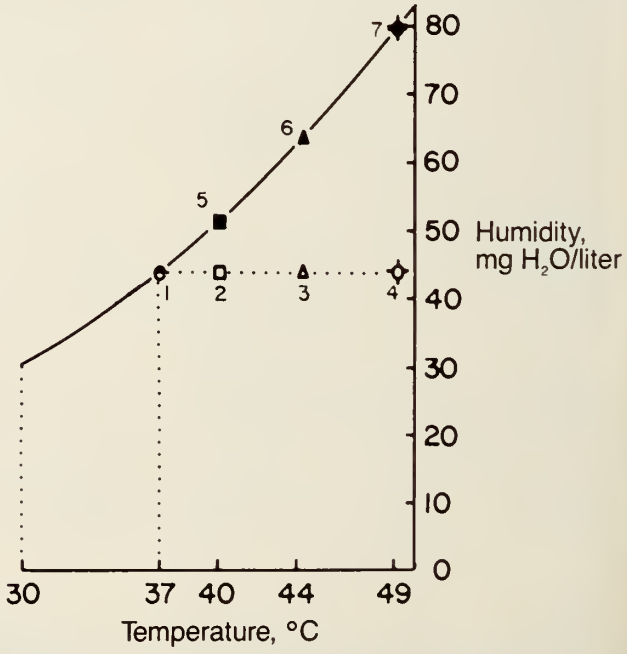

Figure 2.—The graph shows the temperature and absolute humidities of seven air conditions tested. Conditions 1 through 4 all have water contents of 44 mg H_2O per liter with temperatures of 37°C, 40°C, 44°C, and 49°C (98.6°F, 104°F, 111°F, and 120°F), respectively. Conditions 5 through 7 have temperatures corresponding to conditions 2 through 4—that is, 40°C, 44°C, and 49°C—but have 100% relative humidity.

subject briefly (10 to 15 seconds) removed the mouthpiece to clear oropharyngeal secretions. Three to five measurements of the FRC and SG_{aw} were then done within 90 seconds, followed by two forced expiratory maneuvers. Measurements were repeated between the 5th and 6th, the 10th and 11th, and 20th and 21st minutes following the hyperventilation challenge. Following the hyperventilation challenge, patients breathed ambient air during all testing.

Statistical Methods

The mean of each set of three to five SG_{aw} and FRC determinations was used in the statistical analysis. The better of each pair of FVC, FEV_1, and $FEF_{25-75\%}$ measurements was used. The influence of time, humidity, and temperature on changes in the SG_{aw}, FRC, FVC, FEV_1, and $FEF_{25-75\%}$ was determined using a three-way analysis of variance with individual comparisons made by contrasts.[14] The Student's *t* test for paired variates was applied to examine changes in the SG_{aw}, FRC, FVC, FEV_1, and $FEF_{25-75\%}$ at the same temperature but varying humidity. Linear regression was used to correlate the change in the SG_{aw} (ΔSG_{aw}) at one minute and the humidity.

Results

With the exception of condition 3 (44°C [111°F], 44 mg H_2O per liter), all conditions caused an abrupt, immediate fall in the SG_{aw}—that is, seen at one minute. At all times of testing, there was no difference seen in the SG_{aw} with conditions of the same water content (44 mg H_2O per liter) but varying temperatures ($P > .05$). When both temperature and humidity were increased together, however, there was a fall in the SG_{aw} that was pronounced at the time of first testing, with recovery thereafter (Figure 3).

Small changes were noted in the spirometric indices (Table 2 and Figure 3). A small bronchodilatory effect was seen with condition 3 (44°C, 44 mg H_2O per liter) in the FEV_1 (Figure 3). In comparing conditions of the same temperature but different water content (100% saturated or partially saturated—44 mg H_2O per liter), conditions at 44°C (conditions 3 and 6) were significantly different, both in the FEV_1 ($P < .05$) and the SG_{aw} ($P < .005$; Figure 3).

With conditions with 100% relative humidity—that is, conditions 5, 6, and 7—the maximal fall in the SG_{aw} was seen at the one-minute observation. It appears that there is a linear correlation between the mean ΔSG_{aw} observed at one minute and the humidity (Figure 4; $r = .09$, $P < .01$).

Discussion

These results suggest that the water content above 44 mg per liter—that is, fully saturated air above body temperature—may be detrimental to patients with asthma. A beneficial effect is seen when the temperature is raised slightly, to 44°C, but the water content remains that of the body temperature fully saturated (44 mg H_2O per liter). A progressively detrimental effect is observed as the water content is increased.

The disproportionate response in the SG_{aw} versus spirometric indices suggests that the proximal airways may have experienced the bulk of the detrimental effect. Because spirometry was always done after the initial SG_{aw} measurement, it is possible that the apparently disproportionate effect is partially explained by a waning transient bronchoconstriction. Another possibility is that the deep breaths associated with doing spirometry may partially reverse the observed bronchospasm. The SG_{aw} and spirometric data, however, also differed regarding the time course of response in that the maximal decrease in the SG_{aw} occurred at 1 minute whereas the detrimental spirographic effects persisted unchanged throughout the 20-minute period of observation.

Because water was progressively added to the inspirate, a linear relationship of the ΔSG_{aw} against increasing the water content of the inspirate was seen at the time of the first testing. If one extrapolates that linear relationship, the point at which the ΔSG_{aw} intersects the X axis would be the abso-

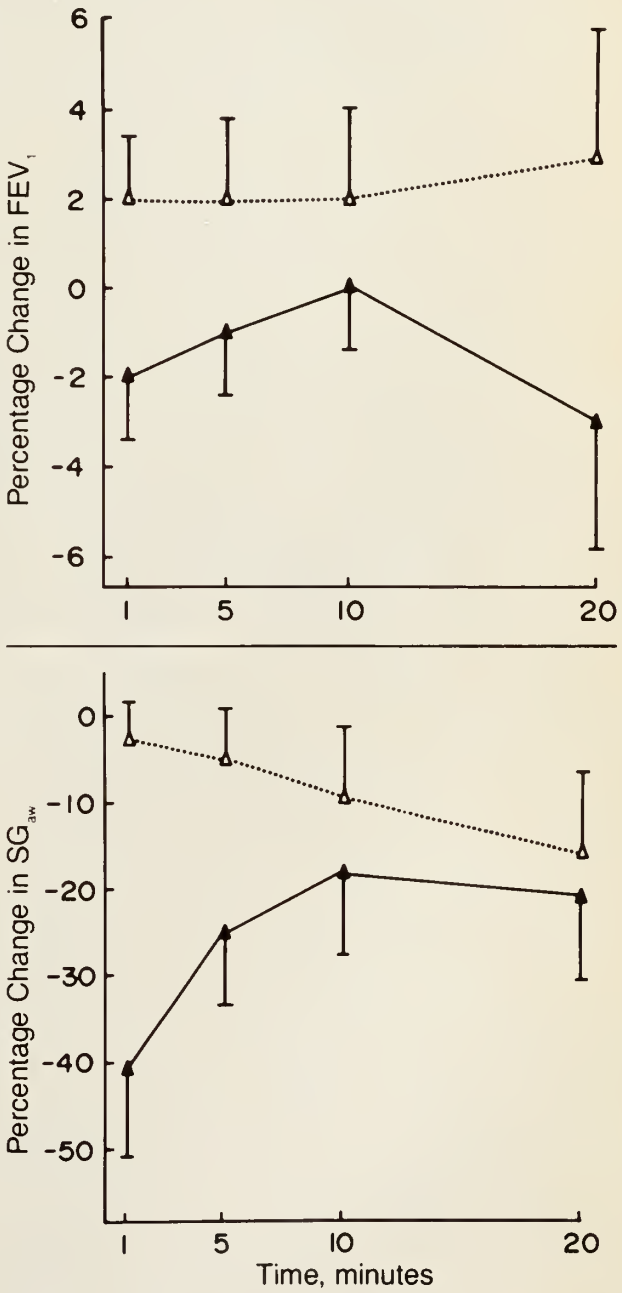

Figure 3.—The graphs show the mean percentage changes in **(top)** the forced expiratory volume in 1 second (FEV_1) and **(bottom)** the specific airway conductance (SG_{aw}) from baseline at 1, 5, 10, and 20 minutes after hyperventilation challenge in 8 subjects with asthma. Δ = condition 3 (44°C [111°F], 44 mg H_2O per liter); ▲ = condition 6 (44°C, 100% relative humidity). At all times of testing, condition 3 differs from condition 6 in both the FEV_1 and the SG_{aw}.

TABLE 2.—*Change in Pulmonary Function Indices After Inhalation of 7 Different Air Conditions Over Time**

Air Condition†	ΔFVC, liters—Minutes				ΔFEF$_{25-75\%}$, liters/s—Minutes				ΔFRC, liters—Minutes			
	1	5	10	20	1	5	10	20	1	5	10	20
1	−1±1	0±1	−2±1	−2±1	+1±5	−2±5	− 3±5	− 2±7	+1±2	−2±2	−2±2	−4±3
2	+1±1	+1±1	+1±1	0±1	−5±2	−8±4	− 6±4	−12±7	−1±3	+2±3	+1±1	+1±1
3	+2±1	+1±1	+1±1	+1±1	+3±4	+5±6	+ 2±4	+ 6±7	−2±2	−4±2	−3±2	−4±3
4	−2±1	0±1	−3±2	−3±1	−1±4	−4±5	−10±5	− 5±7	−1±2	−3±2	−2±2	−4±2
5	0±1	0±1	0±1	−2±1	−9±2	−1±4	− 8±5	− 7±5	+1±3	−4±1	0±3	−3±3
6	+1±1	+1±1	0±1	−2±1	−8±3	−5±3	0±3	− 6±6	+5±3	+1±3	−2±2	−1±2
7	0±1	−1±1	0±1	+1±1	−9±2	−4±4	+ 3±3	− 7±3	+5±3	−3±3	−1±4	−6±4

FEF$_{25-75\%}$=forced expiratory flow rate measured between 25% and 75% of total vital capacity, FRC=functional residual capacity, FVC=forced vital capacity

*Mean ± standard error of the mean.
†See Table 1 for description of air conditions.

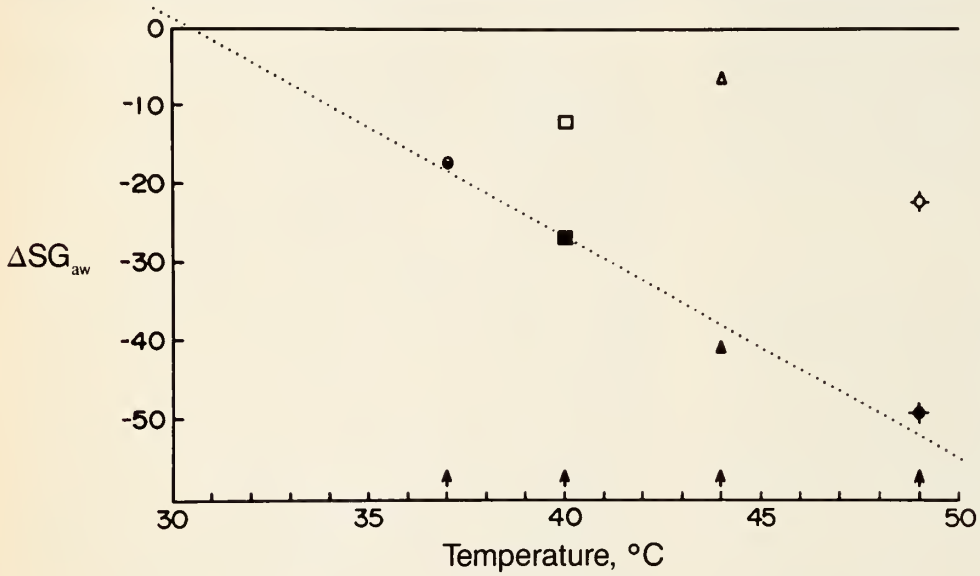

Figure 4.—The graph shows the mean change in the specific airway conductance (ΔSG$_{aw}$) of 8 subjects with asthma at 1 minute after a hyperventilation challenge. The solid symbols indicate fully saturated conditions (see Figure 2 for complete explanation). The dotted line is an extrapolation of the fully saturated data points through the baseline SG$_{aw}$. Where these lines intersect—that is, 30.3°C (86.5°F)—represents a water content of 30 mg H_2O per liter at 100% relative humidity.

lute water content of 30 mg H_2O per liter, which is the 100% relative humidity of 30.3°C. We speculate that inspired air carrying 30 mg H_2O per liter would have no detrimental effect. Moreover, the optimal temperature by our present study is about 44°C. When a person with asthma inhales air of 44°C and 30 mg H_2O per liter, a bronchodilator effect may occur.

We previously showed a mild (10%) improvement in airway conductance when the temperature and heat content of the inspirate were increased in isocapneically hyperventilating normal subjects.[9] More pronounced bronchodilation might have occurred if the inhaled water content had been less than 44 mg H_2O per liter. Moreover, in vitro, bronchial smooth muscle relaxes when examined in an isotonic solution of 40°C.[15]

Although care was taken to filter preformed droplets from the conditioned airstream, it is possible that small water particles form in the upper airway as the hot humid air is cooled to body temperatures. These particles may constitute an irritant stimulus acting on vagal receptors,[15-17] possibly explaining the maximal immediate detrimental effect in the ΔSG$_{aw}$.

An alternative mechanism by which the humid conditions may cause bronchospasm is by water depositing on the respiratory mucosa, rendering it hypo-osmolar. When cold air is breathed, the respiratory tract becomes hyperosmolar as the cold dry air evaporates water from the mucosa[18] and maximal bronchospasm is observed after several minutes of hyperventilation.[19] Thus, the time course of hypo-osmolar conditions appears to be different from the response observed in this study. Supersaturated conditions may deposit water proximally, and hypo-osmolality is seen only in the proximal airways, thereby stimulating an immediate irritant effect. With cold air hyperventilation, hyperosmolality may be seen throughout the respiratory mucosa causing release of mediators and hence a delayed response in bronchospasm.[20]

In summary, we have shown that a limited rise in the air temperature is not detrimental to persons with asthma when the water content is held equivalent to fully saturated body conditions. Moreover, we speculate that a water content of less than 44 mg H_2O per liter would be optimal. Because of its short-lived time course and disproportionate impact on the SG$_{aw}$, the detrimental effect of brief exposures to air supersaturated relative to the body temperature seems irritant in nature. Such irritation, however, could act as the trigger for a bronchospastic episode. The effect of a more prolonged exposure is currently unknown. Based on the data presented in this report, we recommend that inhaled water concentration not exceeding 44 mg H_2O per liter be used in patients with asthma.

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Spinal Headache

SPINAL ANESTHESIA CAN CAUSE HEADACHES. I think we should look a little bit at the characteristics of those headaches. First of all, they are due to decreased intracranial pressure due to loss of fluid from the subarachnoid space. What happens then is that when a patient assumes an erect position, the brain no longer has its normal buoyancy and tends, with gravity, to be pulled down, putting pressure on the meninges and causing a headache. Lie flat and the headache will go away. Usually it's very characteristic in that it comes on with sitting up and it goes away with lying down. It can be a frontal headache, it can be an occipital headache, it can be a nuchal headache. And especially, if your patient has a nuchal headache with rigidity, you're going to start being concerned, as you normally would, with meningitis. Then you have a differential diagnosis that you have to deal with because it would be reasonable to think the patient might have meningitis: you just put a foreign body in their subarachnoid space. It doesn't happen very often—it's very rare these days with spinal anesthesia—but it leaves us something to think about. Usually, these headaches have relatively immediate onsets, but onset can be up to six days postoperatively. The headaches have, usually, self-limiting courses—3 to 4 days—but they may go up to 2 weeks. Some have been reported to last for months.

—JOSEPH L. SELTZER, MD

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Causalgic Form of Postphlebitic Syndrome

A Variety of Reflex Sympathetic Dystrophy Caused by Acute Deep Thrombophlebitis

THEODORE B. MASSELL, MD, *Los Angeles*

The causalgic form of the postphlebitic syndrome or reflex sympathetic dystrophy resulting from acute deep thrombophlebitis is a relatively uncommon and, unfortunately, frequently unrecognized form of the postphlebitic syndrome. The usual signs of venous insufficiency are minimal, but severe burning pain is characteristic, usually increased by dependency. The diagnosis is confirmed by phlebography and the response to a lumbar sympathetic block. A lumbar sympathectomy produces permanent pain relief.

(Massell TB: Causalgic form of postphlebitic syndrome—A variety of reflex sympathetic dystrophy caused by acute deep thrombophlebitis. West J Med 1988 Sep; 149:294-295)

In 1945, a number of patients were admitted from medical facilities overseas to the DeWitt General Hospital, a United States Army vascular surgical center, for the treatment of the consequences of acute deep thrombophlebitis of the lower extremities. Five of these patients showed little or none of the usual signs of the postphlebitic syndrome—edema or venous stasis changes—but they all complained of unusual lower extremity pain. The notable subjective pain with a paucity of objective findings led to a suspicion by the surgical staff of some degree of malingering. When a phlebography was done, the existence of the postphlebitic syndrome was established in every case. It was observed that all of these patients manifested high vasomotor tone, usually greater in the affected lower extremity.

Because of the resemblance to causalgia, the therapeutic effect of a lumbar sympathetic block using procaine hydrochloride was tested. In each instance, striking relief of pain was reported that lasted several hours after the vasomotor effect of the block had disappeared. Two more blocks produced more striking relief in one case so that the pain seemed permanently relieved. The response to repeated blocks was not lasting in the other four cases, but a lumbar sympathectomy with removal of ganglia 1, 2, and 3 provided permanent pain relief in each case.

Since the end of World War II, I have seen several hundred patients with the postphlebitic syndrome. Among this rather large number, 14 have had the causalgic form first noted in the Army hospital in 1945. While this form of a postphlebitic state is relatively uncommon, it is not so rare as to be unrecognized. Nevertheless, only one of seven excellent monographs in vascular surgery,[1-7] that by Bergan and Yao,[6] mentions the syndrome. As recently as September 1987, a review of the reflex sympathetic dystrophy syndrome by Smith and Campbell listed 22 precipitating events or conditions associated with reflex sympathetic dystrophy but did not include acute deep thrombophlebitis or the postphlebitic syndrome.[8] Because the causalgic form of the postphlebitic syndrome seems too little known, this review is presented.

Clinical Features

- Usually a patient has a history of acute deep thrombophlebitis of a lower extremity in which treatment was delayed or inadequate.
- The chief complaint is severe burning pain in the extremity below the knee. The usual symptoms of venous insufficiency are slight or absent.
- An objective examination reveals high vasomotor tone in both lower extremities, greater on the affected side. Calf tenderness is frequent without the other signs attributed to acute deep thrombophlebitis. There may be some edema, but the skin changes of chronic venous insufficiency are absent.
- A plain x-ray film of the bones in the extremity will show diffuse atrophy in about half the cases (6 of 14). The spotty atrophy of Sudeck's sympathetic dystrophy is not encountered.
- A lumbar sympathetic block with a local anesthetic produces striking and sustained relief of pain lasting several hours longer than the thermal effect of the block. In some cases, a second or a third block may produce a permanent relief of pain. Most patients report a shorter duration of analgesia with repeated blocks but obtain permanent relief from a surgical sympathectomy with the removal of lumbar ganglia 1, 2, and 3. After the sympathectomy, there may be a slight increase in the manifestations of venous insufficiency that respond to the usual program of elastic support, avoiding excessive static dependency, nocturnal foot elevation, and appropriate exercise.

The following cases are characteristic:

Reports of Cases

Case 1

The patient, a 28-year-old woman, was delivered of her second baby without obvious complications and was dis-

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charged from hospital on her fourth postpartum day. No untoward symptoms were noted during her hospital stay, but the nursing records showed a labile tachycardia from 72 to 110 per minute each day on the second and third day after delivery. On the seventh postpartum day, because of pain in her lower extremity, she presented at a hospital emergency department where a painfully swollen left lower leg was reported with much calf tenderness and a positive Homans' sign. A phlebogram showed thrombosis of all of the venous channels below the knee with extension into the distal femoral vein. Heparin was administered for seven days at a subclinical dose while the patient was kept on bed rest with the lower extremities elevated. The edema subsided, but the pain persisted. She was discharged to wear elastic stockings and to take 5 mg of warfarin sodium per day.

Over the course of several weeks, increased pain developed in the distal extremity and the patient observed cyanosis and coldness of the affected foot. She was unaware of any edema. Several months postpartum, a vascular surgeon observed no edema or venostasis changes but found that the affected extremity was 3 to 4 degrees cooler than the normal leg. There was much tenderness in the distal calf and ankle area. Comparative x-ray films of the lower extremities showed diffuse atrophy of all the bones below the knee on the left. A lumbar sympathetic block produced pain relief for about 12 hours, but a second block was less effective. A lumbar sympathectomy was followed by complete and permanent relief of pain. The patient was fitted with a heavy knee-length elastic stocking, advised to sleep with her feet 15 cm (6 in) higher than her head, and to return gradually to her normal occupation.

Case 2

The patient, a 35-year-old male accountant and an enthusiastic runner, had tendinitis develop in one ankle for which an orthopedist applied a short cast. At first, the pain behind the ankle subsided, but about the tenth day after the cast was applied, he was awakened from sleep by severe calf pain. The following day, examination showed tenderness deep in the calf, a positive Homans' sign and some slight cyanosis. Ibuprofen was prescribed, along with elevation of the leg and the application of local heat. An examination two days later revealed essentially the same findings. The orthopedist discussed phlebography with the patient, but advised against it because of the alleged hazard of an invasive procedure. He sent the patient home on the same therapeutic regimen.

About two weeks later, increasing pain with upward extension into the thigh caused the patient to go to the emergency department of a local hospital. The emergency physician found considerable edema, a positive Homans' sign, dependent cyanosis, and engorgement of the superficial veins. A phlebogram showed obliteration of all the normal deep veins except the profunda femoris almost to the groin. The patient was admitted to hospital for two weeks on the usual regimen for acute deep thrombophlebitis. At the time of discharge, he was free of edema but had continued pain in his calf that in a few weeks became a severe burning whenever the leg was dependent.

Nine months after the acute deep vein thrombosis began, a vascular surgeon had the impression of reflex sympathetic dystrophy due to thrombophlebitis. A lumbar sympathetic block confirmed the diagnosis by providing several days of complete relief of the burning pain, but a second and a third block each provided progressively shorter pain relief. The patient then had a lumbar sympathectomy and left the hospital on the third postoperative day using a heavy knee-length elastic stocking and maintaining the usual program for venous insufficiency. With progressive exercise and then the resumption of running, he was able to resume his normal activity of running a mile or more without any leg discomfort.

Discussion

Acute deep thrombophlebitis is followed by organization of the venous thrombi and scar tissue formation with splitting of the contracting scar, so that much vein lumen is restored as a narrow irregular passage without functioning valves. The postphlebitic state results in venous insufficiency usually with the manifestations of edema increased by passive dependency, pigmentation in the distal extremity, fibrosis of the subcutaneous tissue, and, too often, stasis dermatitis and ulceration. Most patients with a postphlebitic state have little pain—only mild aching in the dependent position—as long as the skin is intact. Some patients are bothered by nocturnal cramping in the calf, and some become aware of venous claudication with exercise.

In only a few patients does the acute deep thrombophlebitis and the subsequent postphlebitic state produce the mechanism of sympathetic reflex dystrophy. The reasons are not understood. These patients usually show very few or none of the usual symptoms and signs of venous insufficiency.

The only common denominator in the small group of 14 cases of this report was the lack of prompt, vigorous treatment of the acute thrombophlebitis so that there was an extensive loss of venous valves. Ordinarily these patients should have much evidence of venous insufficiency rather than involvement of the sympathetic reflex pain mechanism without obvious signs of venous insufficiency.

The association of a disturbed emotional state with reflex sympathetic dystrophy is well known. That association was observed in most of the patients in this report, but the emotional disturbance in each case seemed to subside after the pain was relieved.

The only effective therapy in my experience involved an attack on the sympathetic innervation of the extremity. In some of the early cases, medical treatment with sympathetic inhibitor drugs was tried without success. More recently, some patients with other forms of reflex sympathetic dystrophy were given corticosteroids, but the response was so poor that this form of treatment was not considered in patients with the causalgic postphlebitic syndrome.

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Clinical Evaluation and Use of Urine Screening for Drug Abuse

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Urine drug screening is indicated to evaluate patients who show mental status or behavioral changes and to monitor the abstinence of drug abusers. The appropriate timing for collecting urine specimens may vary depending on the suspected drug of abuse and on laboratory factors. Laboratories use a variety of techniques to do urine screens, and these must be understood by clinicians ordering the screens to interpret results correctly. In treating drug-abusing patients, clinicians must apply structured reinforcement in conjunction with urine screen results to aid patients in achieving abstinence.

(Saxon AJ, Calsyn DA, Haver VM, et al: Clinical evaluation and use of urine screening for drug abuse. West J Med 1988 Sep; 149:296-303)

Recently there has been a dramatic increase in the frequency with which urine screening is used to detect drug abuse. Not only physicians possess the prerogative of ordering this type of laboratory examination, but law enforcement officials and employers, among others, have the option as well. In the midst of the current national furor over urine testing, the technical and clinical knowledge essential to make appropriate use of the information supplied by the tests often gets obscured. It remains incumbent on physicians of all specialties who may treat in their practice patients with substance use disorders to comprehend fully all technical and clinical facets of the use of urine screening.

Urine screening is a tripartite procedure involving the collection of specimens, a laboratory analysis, and the clinical application of the laboratory results. After reviewing the indications for doing a urine drug screen, we will examine in detail all three aspects of the procedure. We will offer general guidelines for the use of urine screens that clinicians, particularly primary care providers, can tailor to fit their diagnostic and treatment goals with individual patients in specific situations.

Indications for Urine Screening

Urine drug screens may be ordered for diagnostic or treatment purposes, or both simultaneously. Probably the most common area in which they deserve consideration as a diagnostic tool is in evaluating mental status changes. Even in the elderly, who may not be using illicit drugs, urine screening may uncover an inappropriate use of prescription medications or over-the-counter drugs such as phenylpropanolamine or scopolamine hydrobromide as causative factors in delirium, dementia, or depression.[1] Similarly, urine screening should be done for all adolescents or young adults who present with school difficulties, behavior problems, or unexplained medical problems to rule out drug abuse as an etiologic concern.[2] Other indications for the diagnostic use of urine screens include a newly developing psychosis, an unexpected deterioration in occupational or social functioning, and, of course, to identify the specific substance a known drug abuser has taken.

Using urine screening in the workplace to detect psychoactive substance use remains a hotly controversial issue. The federal government has initiated a program for some of its employees to screen for the use of marijuana, cocaine, amphetamines, opiates, and phencyclidine. It involves the nonobserved collection of specimens and does not screen for alcohol or prescription drug use. Exponents of the plan contend that the procedure will cost $15 to $25 per specimen, while critics insist that proper testing might actually run from $100 to $300 per specimen. Furthermore, no published research has yet shown that urine screening enhances workplace safety. Private industries have launched screening programs without any requirement to adhere to legislated guidelines. Extensive litigation is in process that challenges the legality of urine screening. At present, any definitive statement about the value of workplace screening must await a more thorough scientific investigation.[3]

Once urine screens have aided in achieving a diagnosis, they can evolve into a powerful treatment tool. Their optimal potency in treatment relies on a grasp of collection procedures and laboratory techniques.

Collecting Specimens

Central to the actual physical collection of specimens is the obvious though potentially overlooked fact that the act of providing the specimen must be carefully observed by a reliable party from urethra to container. Urine from a source other than the person on whom the screening is being done can easily be substituted, or the specimen can be diluted or adulterated.[4] If direct observation is judged inadvisable, requesting donors to leave coats, other outer garments, and personal belongings outside the collection room can help prevent the substitution of false specimens. The absence of a sink in the collection room and the use of a bluing agent to

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ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
EIA = enzyme immunoassay
FPIA = fluorescence polarization immunoassay
GC = gas chromatography
HPLC = high-performance liquid chromatography
MS = mass spectrometry
RIA = radioimmunoassay
THC = tetrahydrocannabinol
TLC = thin-layer chromatography

color the toilet water can pose a barrier to diluting a specimen. Collection personnel can inspect the urine color and measure its temperature to verify specimen validity. Laboratory personnel can check the urine pH and specific gravity to discover adulteration or dilution.[5] Immediately after obtaining a filled specimen container, collection personnel must, in view of the donor, affix a label bearing the donor's name or identification number (or both). Locked storage of the specimens to prevent possible tampering and refrigeration at 4°C (39°F) if more than several hours elapse before conveying to the laboratory guarantee the optimal integrity of the specimen.[5] Of course, personnel handling urine specimens should wear disposable rubber gloves and practice adequate hand washing to protect themselves from possible exposure to infectious agents in urine.[6]

A first morning urine specimen, being the most concentrated, represents the ideal specimen. An actual urine drug concentration depends, however, on the dose, the route of administration, the time since administration, and a person's physiologic state,[7(p80)] so scheduling the appropriate frequency of specimen collection remains the more complex issue. In the early 1960s, at the inception of methadone maintenance—the original form of structured drug abuse treatment—urine specimens were collected daily.[8] Limitations of expense and convenience make this theoretically ideal collection schedule unfeasible. Establishing a collection frequency with regard to the specific drugs one hopes to detect, the particular characteristics of a patient, and the types of laboratory tests available—discussed later—supplies a more reasonable approach to this problem. For example, many methadone programs in the 1970s altered their collection schedule to a random once-a-week collection.[9] In this paradigm, patients must give one specimen per week without knowing in advance on which day it will be required. The rationale behind this change relates to recognizing that a serious pattern of opiate use in a primary opiate abuser almost inevitably leads to daily use to prevent physiologic withdrawal.[10] Continuous drug use will not escape exposure by once-per-week screening.

Harford and Kleber also showed that money and time could be saved by implementing screening at random intervals, which offered the ability to detect illicit opiate use in methadone patients superior to that of random weekly screening.[11] In random-interval screening, patients incur an obligation to provide specimens on an average of only two or three times per month as compared with random weekly screening that requires four or more specimens per month. In random-interval screening, however, patients remain at risk to give a specimen on every single day of the month, even potentially on two consecutive days. This feature eliminates the "safe" periods inherent in random weekly screening—the days remaining in a given week after a patient has provided a specimen and knows screening will not occur again until the following week. Thus, in general, greater randomizing of collection schedules enhances the capacity to detect drug use.

In contrast to opiate addicts, primary stimulant abusers often self-administer their drugs in binges with intercurrent periods of abstinence.[10] Cocaine poses a particular problem in conjunction with this phenomenon of binging because of its brief half-life of 40 to 80 minutes.[12] Because the drug and its metabolites are excreted so rapidly, they are present in urine for a relatively short period after the drug is administered. With standard laboratory methods, therefore, urine must be sampled at least two to three times a week to reliably detect cocaine use.[13] Even without randomization, three times per week collection will not likely miss cocaine use. Amphetamines, which have a longer half-life of 6 to 12 hours,[14] may appear in urine for more than two days following their administration.[15] Screening once or twice a week, particularly if done randomly, should prove sufficient.

At the other end of the spectrum lies marijuana. The major psychoactive alkaloid in marijuana, tetrahydrocannabinol (THC), and its metabolites display high lipid solubility and can be present in the body and the urine for more than a week after a single exposure and for as long as four to six weeks after continuous heavy use.[16] In this situation, a urine screen positive for marijuana merely indicates recent use and does not quantify or date the use. To screen for marijuana any more regularly than once or, at most, twice per month simply wastes money. Quantitative blood concentrations may prove more useful in a clinical situation mandating a diagnosis of acute marijuana intoxication.[4]

The benzodiazepines occupy the middle of the continuum. Like THC, benzodiazepines are highly lipid soluble, but different agents have widely varying half-lives and potencies.[17] Longer acting and less powerful drugs on a milligram-for-milligram basis such as diazepam or chlordiazepoxide may appear in urine for more than a week after a single ingestion.[15] Quantities of low-milligram, short-half-life drugs, such as triazolam, sufficient to be detected in urine may disappear after 24 hours or less. In general, then, adequate screening for benzodiazepines can occur weekly or even every two weeks in some cases. Concerns over the

TABLE 1.—*Detection Limits for Urine Drug Testing*

Drug	*Dose, mg*	*Detection Time, hr*	*Screening Frequency, ×/wk*
Amphetamines	30	1 to 120	1 to 2
Barbiturates			
Short-acting	100	At least 4.5‡	1 to 2
Phenobarbital	30	6 to 24	1 to 2
Benzodiazepines			
Long-acting—diazepam	10	7‡	1
Short-acting—triazolam	0.5	24	2 to 3
Cocaine	250	8 to 48	2 to 3
Methadone	40	7.5 to 56	2 to 3
Methaqualone	150	60	1 to 2
Morphine—opiates (IV)	10	84	1
THC metabolites	*	7 to 34‡	§
	†	6 to 81‡	

IV=intravenous administration, THC=tetrahydrocannabinol

*Marijuana use once per week.
†Marijuana use daily
‡Days.
§Once a month.

abuse of agents with short half-lives, however, should prompt screening several times per week on a random basis. Table 1 summarizes the detection limits and suggested screening frequency for commonly abused drugs.

Laboratory Analysis of Specimens

While effective urine screening depends entirely on laboratory technique, laboratory analysis can be fraught with pitfalls. Reports through the years have shown that many laboratories doing urine screening provide grossly inaccurate results.[18-20] In 1985 the Centers for Disease Control (CDC) did a blind examination of 13 laboratories serving 262 methadone maintenance clinics.[21] They found unacceptably high false-negative rates averaging 59% for barbiturates, 69% for amphetamines, 12% for methadone, 64% for cocaine, and 62% for morphine. Average false-positive rates were not as dismal, but some laboratories did as poorly as 37% false-positive for methadone. The CDC researchers calculate that as much as $75.6 million is wasted annually on erroneous drug testing results. This phenomenon of poor performance can be explained by an understanding of the various laboratory procedures that are used to analyze specimens, the cross-reactions with other prescription or nonprescription medications that can occur, and the uneven quality of performance in each particular laboratory. Knowledge of these factors helps to eliminate much of the disruption that can ensue when practitioners attempt to apply urine screen results clinically.

Laboratories use two types of tests, screening and confirmatory, for detecting drugs in urine. Screening tests, designed to be simple, efficient, inexpensive, and rapid, generally are the initial step carried out on a large number of specimens. Confirmatory tests are reserved for those specimens found positive with the screening test. Confirmatory tests tend to be more complex and labor-intensive than screening tests.

As with all chemical laboratory tests, decisions must be made as to what test values will be considered abnormal or "positive." The threshold concentration, or "cutoff," used in screening tests must be carefully selected to obtain the desired sensitivity and precision. The threshold concentration differs from the sensitivity or detection limit of an assay. This latter value refers to the absolute lowest detectable analyte concentration. Threshold concentrations define the drug level at which specimens will be called positive and are usually set at a level higher than the detection limit of the assay to avoid imprecision that may occur near the detection limit. For example, the cutoff value for a benzodiazepine radioimmunoassay (RIA) can be set at 100 ng per ml, well above its detection limit of 5 ng per ml.[22] Table 2 lists the threshold concentrations for selected drugs, analyzed by three common types of screening assays. The selection of the appropriate cutoff value in a given method will depend on a particular assay's precision and accuracy.

TABLE 2.—*Threshold Concentrations, in μg/ml Urine*

Drug	*Enzyme Immunoassay*	*Radio-immunoassay**	*Thin-Layer Chromatography†*
Barbiturates	0.3-2.0	0.2-3.4	0.5-1.0
Amphetamines	0.3-1.0	1.0	0.3-0.5
Methadone	0.3	...	0.5
Benzodiazepines	0.3-2.0	0.1	1.0
Propoxyphene hydrochloride	0.3	...	0.5
Phencyclidine	0.08	0.025-0.10	0.1-0.2
Cocaine			
Parent	25.0	0.45	1.0
Benzoylecgonine—cocaine metabolite	0.3	0.3	1.0
Opiates—morphine	0.3	0.3	0.25
Codeine	1.0	0.16	0.25
Cannabinoids—as total metabolites	0.1	0.1	0.075-0.1
Methaqualone	0.3	0.75	1.0

*Abuscreen.
†"Traditional" thin-layer chromatography; sensitivity varies widely, depending on the system used

A lower working detection limit obviously improves the yield of true-positive tests but also increases the chance of false-positive tests. If the cutoff point is too low, a confirmatory test may not confirm the results of the screening test. Using a higher threshold reduces the incidence of false-positives but increases the likelihood of false-negative results. The choice of a threshold value may also be influenced by the clinical purpose of the test. For example, establishing a threshold value of 100 ng per ml for marijuana screening will minimize the possibility of a positive result for persons with only a passive exposure to cannabis.[23]

Immunoassays

Enzyme immunoassay (EIA), fluorescence polarization immunoassay (FPIA), and RIA are generally preferred for the initial screening. All types of immunoassays depend on the principle of competition between a marked or labeled antigen and an unmarked antigen for binding sites on a specific antibody. For drug detection, the actual drug to be detected serves as the antigen. Therefore, a separate immunoassay procedure must be done for each class of drugs to be detected.

In the enzyme immunoassay system, the marker is an enzyme to which the analyte (drug) molecule has been permanently attached. When the enzyme acts on its substrate in solution, this chemical reaction causes an absorbance change in the solution that can be measured in a spectrophotometer. To carry out the EIA, a sample from a urine specimen that is being checked is placed in a solution along with the substrate and antibodies against a particular drug. At this point, the enzyme-drug complex is added to the solution. If the urine specimen contains none of the drug in question, the antibody will bind to the enzyme-drug complex, rendering the enzyme inactive; the enzyme cannot act on the substrate, and no change in absorbance is noted. Thus, a lack of change in absorbance equates with a negative urine assay.[24] If, however, the urine specimen did contain some of the drug, the drug would bind the antibody to it, preventing the antibody from binding to the enzyme-drug complex; the enzyme would retain activity and the chemical reaction would ensue, in turn causing an increase in light absorbance as measured by the spectrophotometer. In other words, an increase in absorbance means a positive assay.[24]

FPIA assays are based on a similar competitive principle. In this case, the marker is a fluorescein-labeled drug and the system measures the fluorescence polarization resulting from the binding of this tracer to specific antibodies. When more of this marker is bound to antibody—that is, when urine drug concentrations are low—the amount of polarized light emitted will be high because this large complex cannot

tumble freely in solution. When urine drug levels are high, tracer is displaced from the antibody and this small molecule tumbles freely in solution, resulting in less polarized light emitted.[25(p39)]

These immunoassay reagents cost about $1 to $4 per test for each specific drug. Assays have been adapted to several types of batch or random-access analyzers, which allow a large number of specimens to be processed simply and automatically with objective results obtained by the instrument.

Radioimmunoassay, like EIA and FPIA, uses a competitive binding principle but with a radioactive isotope as its marker. The radioactive isotope is bound to a molecule of the drug to be detected and placed in a solution with antibodies to the drug and a specimen of urine. If the urine specimen contains none of the questioned drug, the antibodies will bind to the radioactively labeled drug. Should the urine contain the drug, the free drug will compete with the radioactively labeled drug for antibody binding. In either case the solution undergoes centrifugation until the antigen-antibody complexes precipitate out. After removing the supernatant—a physical separation step not required in EIA or FPIA—a gamma counter measures the radioactivity in the precipitant.[26] The precipitant from a drug-negative specimen will show a high amount of radioactivity because most of the radioactively labeled drug was bound to antibody and precipitated. Conversely, illicit drug, when present, will bind antibody in place of the radioactively labeled drug, and the antigen-antibody complexes that precipitate will show proportionally less radioactivity. Thus, radioactivity counts translate into a quantitative urine drug concentration. Because of the radioactive component, careful monitoring of both personnel and laboratory facilities is required to ensure safe handling, storage, and disposal.

The antibodies used in many immunoassays are not specific for single drugs but cross-react with chemically related drugs and metabolites. For example, the amphetamine EIA will detect not only amphetamine and methamphetamine but also phenylpropanolamine and ephedrine/pseudoephedrine,[27] providing a false-positive result. False-positives may also result from a carryover of a preceding specimen that tested strongly positive.[24]

Thin-layer chromatography (TLC) often functions as an initial screen and, if used appropriately, may also serve to confirm positive immunoassay results. The TLC procedure involves the urine being extracted by an organic solvent, followed by applying of a specimen onto a silica-coated plate. After the plate is immersed in another solvent, various drugs in a sample, depending on their unique solubility, will migrate to different areas of the plate. Spots correlating to the parent drug or its metabolites should appear at a given location on the plate. Small changes in the composition of the developing solvent mixture can result in subtle changes in migration rates. Therefore, reference standards are developed on the same thin-layer plate along with the unknown sample. Spots on the plate from drugs in the unknown specimen can be compared against the standards to aid in identification. Drugs that may migrate to nearby areas can be more precisely identified by immersing the plate in various reagents, which will cause spots representing different drugs to colorize differently, or by examining the plates under ultraviolet light, which allows several drugs to exhibit a characteristic fluorescence.[28]

Advantages of TLC include low cost—about $3 to $4 per specimen to detect all drugs present—and the fact that one test provides a broad screen for a variety of drugs at one time while obviating a reliance on technologically advanced equipment. (A recent research report indicates that EIA reagents may be mixed in a solution simultaneously to provide a comprehensive drug screen like TLC,[29] but this method would require further evaluation before it comes into general use.)

Thin-layer chromatography also has significant disadvantages.[25] It is a labor-intensive and time-consuming technique. It is somewhat subjective because it depends on trained human observers to interpret the visual results. The ability to recognize different metabolite patterns, especially when several drugs are present, requires an experienced technologist. This expertise may vary from laboratory to laboratory or even within laboratories. Occasionally another substance in the urine produces a spot on the chromatogram that either masks or is misinterpreted as the drug in question. Therefore, definitive identification on the basis of a chromogenic reaction, migration, or both, proves impossible.

The proper detection of many benzodiazepines and opiates in urine by TLC—or gas chromatography (GC) or high-performance liquid chromatography (HPLC)—requires a separate hydrolysis step because these drugs are predominantly excreted as their glucuronide metabolites. These metabolites are more polar than the "free" or unconjugated compounds and are not extracted by the organic solvent used in these chromatographic methods. One study graphically shows the importance of this hydrolysis step: 345 urine specimens were tested for opiates by TLC without the hydrolysis step, and also by EIA, which detects the glucuronide metabolites. TLC detected opiates in 95 of the specimens, while EIA found opiates in 200 of the identical specimens.[30]

The stated detection limit for most drugs of abuse analyzed by TLC is approximately 1,000 ng per ml, and TLC generates only qualitative, not quantitative, results. In contrast, EIA systems, because they incorporate a limited set of standards (calibrators), can yield semiquantitative results. Radioimmunoassay and FPIA can be made quantitative because they measure discrete levels along a full standard curve. Many laboratories, however, select a particular threshold level and report results either as positive or negative. For certain drugs, such as cocaine, the immunoassays are more sensitive than TLC. The EIA detection limit for benzoylecgonine, the primary cocaine metabolite, is 300 ng per ml, whereas the detection limit by TLC is 1,000 ng per ml. As a practical example, TLC will detect cocaine metabolites in urine for, at most, 12 to 24 hours after the last use of the drug. Enzyme immunoassay generally detects cocaine for at least 48 hours after its use (Tables 1 and 2).[13]

A confirmatory test—using a more specific method—should be done to verify a positive screening test. Confirmation becomes essential when significant penalties or legal actions will ensue. The confirmatory test ought to be based on a different principle of analysis and be at least as sensitive as the screening test. For example, if the screen were an immunoassay, such as the cannabinoid EIA, the confirmatory technique should use a different methodology—chromatography such as thin-layer, high-performance liquid, or gas—and not another immunoassay such as RIA. The threshold concentration of the confirmatory assay should be set at a concentration consistent with the drug in question,

which may be lower than that used in the preliminary screening. For example, the cannabinoid EIA detects several cannabinoid metabolites and has a threshold of 100 ng per ml; the threshold of the gas chromatography-mass spectrometry (GC-MS) confirmation assay based on the detection of one metabolite, Δ-9-THC-COOH, may be set at 20 ng per ml.[31]

Gas chromatography and high-performance liquid chromatography are used mostly for confirmatory analysis because the procedures are more complex and labor-intensive and do not lend themselves to processing large numbers of specimens. As in TLC, these methods employ a chromatographic separation to allow the identification of unknown drugs in a mixture.[26] In GC a larger volume of urine—5 to 10 ml—is extracted with an organic solvent and the extract is dried down and reconstituted in a small volume of solvent. Minute quantities are then injected into fused silica capillary columns 0.2 to 0.7 mm in diameter and 5 to 100 m in length. The separation results from an equilibrium established between the drug in the mobile or gas phase and drug in the stationary or liquid phase adsorbed on the wall of the column. A differential partition of the drug in these two phases occurs, such that certain drugs will be retained longer than others on the column. A detector observes when the drug emerges from the column, and this retention time helps to identify the drug. The time required to elute any given drug from a GC or HPLC column is not necessarily unique, however, so no single system will suffice for proper drug identification. That is, the retention time alone cannot make a definitive drug identification, and other tests—such as the immunoassay screens—must be done in tandem.

The various types of detectors used in GC analysis influence the test's sensitivity. Flame ionization detectors are conventional and will detect any organic substance. Nitrogen-phosphorus detectors are particularly useful for detecting halogens (chlorine), or nitrogen- or phosphorus-containing compounds. The nitrogen-phosphorus detector response may be 15 to 300 times greater than that of the flame ionization detector for such compounds—cocaine or phencyclidine. Electron capture detectors are also more sensitive, but their use is restricted to compounds (or derivatives) that contain halogens. A flame ionization detector can measure in 1 ml of urine microgram to submicrogram quantities of drug. For particular cases where sensitivity appears inadequate, or if the drug lacks volatility, the drug may need to be chemically altered before being injected into the column.[25] The sensitivity of gas chromatography at least equals and sometimes betters that of the immunoassays, depending on the choice of detector. Clearly, GC sensitivity varies with the specific techniques and equipment employed.

GC-MS uses a mass spectrometer as a detector. It combines the separating capabilities of GC with the sensitivity and specificity of a mass selective detector. In mass spectrometry, compounds (drugs, molecules) undergo ionization to create various-sized fragments. Filtering these fragment ions through electrostatic or magnetic fields, producing what is called a "mass spectrum," permits identification by their mass-to-charge ratio. Every given compound or drug possesses a unique mass spectrum. Reference libraries of mass spectral data are available for identifying unknowns. The ability of GC-MS to couple spectral data with retention time data offers a definitive identification of drugs and affords GC-MS its deserved reputation as the "gold standard" for confirmatory testing. (HPLC, as discussed later, is also a powerful tool when used with a mass spectrometer.)

GC-MS can be operated in two modes. Used when drugs are of sufficiently high concentrations in the urine, the "full scan" mode produces a complete mass spectrum or "fingerprint" of the drug. Operating in the scan mode, GC-MS has a sensitivity comparable to that of conventional GC—that is, where flame ionization or nitrogen-phosphorus detectors are used. The mass spectrometer can also be operated in the selected ion monitoring mode. In this mode, only a few ion fragments characteristic of the drug are monitored. Because the detector spends more time looking for a few ions, the sensitivity increases about tenfold to 100-fold when compared with the "scan" mode. Some specificity is sacrificed because identification is based on a less specific pattern. The combination, however, of a positive immunoassay and a GC-MS result with the proper retention times and three mass ions of the proper intensities will distinguish the compound in question from more than a million other organic compounds.

In high-performance liquid chromatography, which is not as widely used as gas chromatography, the drug equilibrates in a column between two liquid phases.[25] HPLC, too, may use various detectors, including ultraviolet, fluorescent, electrochemical, diode array scanning, or mass spectral. It is also labor-intensive and requires sample preparation as in GC. HPLC, however, can analyze polar compounds that prove unsuitable for GC without being chemically altered. HPLC has found use in the analysis of benzodiazepines, opiates, and tricyclic antidepressants.[32,33] The sensitivity will depend on the particular drug to be analyzed and the choice of detector, but, in general, HPLC also detects microgram to submicrogram levels per milliliter of urine.

Many laboratory facilities are not equipped to do such sophisticated analyses as gas chromatography, HPLC, and mass spectrometry. The instruments are costly to acquire and maintain and complex to run. Analysts must possess a high level of skill and experience with the extraction procedures, in operating the instrument, and in interpreting the data.

An encouraging recent report on the status of drugs-of-abuse testing showed that laboratories can exhibit great accuracy if appropriate screening, confirmatory tests, and threshold values are used.[34] In this study, 47 laboratories were assessed for their accuracy in detecting five drugs of abuse, including opiates, cannabinoids, amphetamines, cocaine, and phencyclidine. The laboratories in the study did both screening and confirmatory testing of all five drug classes, and they were challenged to detect drugs at concentrations at which they normally accept business. The overall accuracy was better than 95%, with a false-negative rate of 0.8% and a false-positive rate of 0.05%.

It is important that clinicians know whether a laboratory does confirmatory testing or preliminary screening only. The specific threshold concentrations used to report positive tests, as well as policies for reporting positive tests detected below these threshold concentrations, should also be known. Such information and the selection of a laboratory involved in an external proficiency testing program will help ensure reliable drug testing.

Clinical Applications

Over the past 20 years, most of the relatively small number of studies that have examined the clinical applica-

tions of urine screening have taken place in methadone maintenance clinics. Patients on a methadone regimen, though mainly primary opiate abusers, will also abuse other drugs such as cocaine[35] and benzodiazepines[36] in addition to heroin. Despite the high prevalence of illicit drug use in this population, many methadone clinics have remained in a quandary over how best to use the positive urine screening reports they receive.[30]

Several studies indicate that merely confronting drug abusers with the objective evidence of their drug use—in the form of urine screening results—has a negligible impact on drug use. For example, in a study cited above,[30] 76 methadone-maintained patients gave weekly random urine specimens that were tested by TLC. Of these patients, 37 also had their urine screened by EIA. EIA had twice the power of detecting illicit opiate use, but over 13 weeks the EIA group displayed illicit drug usage equivalent to the TLC-only group. Thus, a better capability of objectively discovering illicit drug use produced no alteration in this behavior.

Another study confirmed this impression by observing 431 methadone-maintained patients over a year's time.[37] The patients were randomly assigned to a weekly urine-monitored or a totally unmonitored program. Surprise, spot urine specimens obtained from all subjects at various points in the study indicated that no differences in illicit drug use existed between the two groups.

Only one published study has examined the efficacy of urine surveillance by a controlled trial in a non-methadone treatment setting. The patients were primarily opiate or barbiturate abusers. A total of 29 subjects received hospital detoxification before being randomly assigned to one of three treatment groups: outpatient psychotherapy, group or individual, with weekly urinalysis; outpatient psychotherapy without urinalysis; or a waiting list for outpatient treatment. The patients in the weekly urinalysis group were confronted with their detected drug use in therapy sessions. The study ran for three months. By self-report, the urinalysis group decreased their barbiturate use compared with the other groups. More opiate abuse occurred in the urinalysis group than in the non-urinalysis group, however, though this difference did not attain statistical significance. Even these authors conclude that urine surveillance was merely "somewhat helpful" but would have maximal impact if results were "used in some meaningful program contingency."[38]

Other investigators have adopted this notion of contingencies based on the theory that most patients will refuse to relinquish readily the compulsive use of any potently reinforcing drug. Thus, punishments or rewards more powerful than such reinforcing drugs as heroin or cocaine must be used to induce drug abusers to desist from taking drugs. The best verification to date of this concept comes in the form of a study that involved randomly assigning 69 methadone-maintained patients to a "structured" or "unstructured" treatment.[39] Supervised collecting of urine specimens from all patients was done weekly. Repeated positive urine screens led to methadone detoxification for the structured treatment group. The unstructured treatment group received a notification of concern but no specific consequences for positive urine screening. Over a year's time, the former group used fewer illicit drugs and had a superior degree of retention in treatment compared with the latter group.

Stitzer and colleagues over the years have shown in numerous controlled studies that contingent rewards—cash payments, an increase in methadone dosage, extra take-home methadone—for drug-free urine specimens can reduce illicit benzodiazepine, multiple drug, and opiate abuse in methadone patients.[40-42]

At present, not a single scientific study convincingly indicates that urine screening results used in counseling or confrontation motivate most drug abusers to alter their habits. In contrast, experimental data strongly suggest that, in combination with assured punishments for continued drug use—or rewards for abstinence—urine screening becomes a behavioral strategy successful in treating many drug abusers.

The optimal means of establishing and implementing contingencies for illicit drug use remain uncertain, but open trials of a technique called "contingency contracting" point out possibilities to explore. This technique consists of using a written, detailed, personalized contract specifying the precise consequences that a drug abuser will suffer if he or she provides a given number of positive urine specimens. One uncontrolled, open trial used contingency contracting to treat cocaine abusers.[43] Contracts were offered to 67 patients, of whom 32 agreed to contracts that included urine monitoring and exceedingly aversive consequences—such as notifying an employer of the drug use—for the first cocaine-positive urine specimen. Of those accepting contracts, 31 abstained from using cocaine for the length of the mutually agreed on treatment, with 81% remaining for at least three months. Of the 35 refusing contracts, only 9% (3) stayed in treatment and abstained for four weeks. The longest any of the latter group stayed was two months.

One of the authors also looked at contingency contracting with 17 drug-abusing health care professionals.[44] Again, written contracts mandated a severe consequence—loss of professional license—for a single positive urine screening test. Only two persons had their licenses revoked.

Another open trial exploited contingency contracting to treat 21 methadone-maintained patients considered "treatment failures" based on illicit drug use detected by at least 50% positive weekly urine screens over a 60-day period.[45] These patients had no response to any other treatment method before being placed on written contracts specifying methadone detoxification and discharge for any positive urine screens over a 30-day duration. Of the 21 patients, 11 significantly reduced their illicit drug abuse over the span of the contract and over a 60-day follow-up period. Our own recent work confirmed these findings of an improvement in 50% of methadone treatment failures with contingency contracting and further showed that contingency contracts could be routinely and uniformly applied in the nonresearch setting of a large methadone program.[46] Indeed, contingency contracting has become such an established practice that 72% of methadone clinics nationwide use this technique to manage illicit drug use.[47]

For a clinician treating a drug-abusing patient, some practical issues in regard to implementing contingencies arise. First, it may seem incongruous that any patients would submit to agreements that might result in undesirable or unpleasant consequences. Certainly many will not, but others, if approached during a properly chosen interlude of personal anguish or social duress, will mobilize the remaining shreds of their self-respect to place themselves within the bonds of an agreement that will ultimately help to salvage that self-respect. With the terms of the contract immediately codified in writing and signed by the patient, an external object is

created that directly symbolizes to the patient his or her self-respect. The likelihood of chafing against its restrictions is diminished, permitting an appreciation of the support and protection it provides.

A second issue involves what kinds of negative reinforcers to include in a contract. Certainly these must be individually tailored for each patient, but several general areas apply to many people. Crowley[43,44] has suggested that an agreement focus on a person's means of earning a livelihood, such as notifying an employer or professional licensing board if urine screens remain positive. Often less severe consequences may seem appropriate. Among these might be a patient's agreement to be admitted to hospital after a specified number of positive urine screens. Alternatively, the patient might be required to donate a given sum of money to a specified charitable organization for every positive urine screen. In many cases, a patient's family may involve themselves in the contract process, and a temporary marital separation or a temporary eviction of the patient from the home could be the consequence for positive urine screening, with eventual reunion possible after a string of consecutively negative urine screens. Perhaps the most potentially punitive consequence of all would be reporting a patient's continuing drug use to the criminal justice system if that person has already been embroiled in legal difficulties. Future research may elucidate which of these reinforcers or combination of reinforcers works best for which patients.

Finally, many clinicians may feel uneasy enforcing such seemingly draconian measures as treatment expulsion, loss of income, forced hospital admission, loss of family, or incarceration. One must bear in mind that these contingencies forecast precisely the consequences that would ensue in any event from continued drug use as the addict becomes too destabilized to attend treatment or work regularly, must be admitted for the medical complications of drug use, alienates his or her family, or engages in illegal activities to finance drug purchases. Confronting drug abusers at the outset with the predictable results of their behavior may serve to prevent these consequences rather than make them inevitable.

Conclusion

With all the foregoing in mind, it is possible to formulate some general caveats about urine drug screening in clinical practice. A guiding principle is to maintain an awareness of all three steps in the urine screening process—collection, laboratory analysis, and clinical application—and how they intersect. Thus, collection timing and frequency depend on the clinical situation, including the types of drugs a patient may be abusing and the patterns of abuse. They also depend on what type of laboratory analyses are being done: More sensitive laboratory techniques may permit a less frequent collection schedule. Clinicians must obtain information about a specific laboratory that handles the specimens. Not only must clinicians know which laboratory techniques are used, but they must also have some sense of a particular laboratory's reliability at executing these techniques. This knowledge may help to explain possible false-positives or -negatives that fail to fit the clinical features of a case. Because all laboratories are sometimes fallible, and many are frequently so, it remains incumbent on a laboratory to confirm positive results by a different technique and on clinicians to avoid placing too much clinical weight on the results from any single specimen. In specific clinical situations in which the precise timing of drug use or exceptional accuracy are required, a clinician may need to ask the laboratory to use a specified technique or to send the specimen to another facility that can.

A crucial concept in the clinical arena is the frequent failure of urine monitoring and counseling to help drug-abusing patients curtail their addictions. Obtaining a patient's agreement to participate in a urine monitoring program with specified written consequences for positive urine screens may prove an invaluable maneuver in this context.

In a time of escalating drug abuse and the societal concerns it has raised, practitioners will be increasingly called on to evaluate drug-abusing patients and so to order and interpret urine drug screens. Many practitioners, especially those in areas where no drug abuse programs are available, may find themselves treating drug addiction. While much work remains to be done in developing effective treatments for substance abuse, we have attempted to consolidate and make useful the existing knowledge about urine screening that will continue to gain in importance as one of our effective treatment modalities.

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Medical Practice Opinion

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Commission on Quality Care Review of the California Medical Association. The opinions offered are based on training, experience, and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions, or policy statements.*

Pelvic Lymph Node Dissection and Radical Prostatectomy

QUESTION:

Is it accepted urologic practice to stage a pelvic lymph node dissection, with permanent section microscopic analysis, as a separate operation before doing a radical prostatectomy?

OPINION:

The Scientific Advisory Panel on Urology recognizes that there are two medically accepted procedures for performing pelvic lymph node dissection in patients having radical prostatectomy.

Because it is well documented that 10% to 20% of frozen section assays are false-negative—depending on the institution reporting the data—some urologists prefer to stage pelvic lymph node dissection as a separate operation and await the results of permanent section microscopic analysis before proceeding with radical prostatectomy. Other surgeons rely on frozen section assays at the time of dissection to allow immediate prostatectomy, if the lymph nodes are free of disease.

The choice of procedure should be at the surgeon's discretion, taking into account the variables that may exist within individual patients and institutions.

Approved: May 1988

This opinion has been prepared by the CMA Scientific Advisory Panel on Urology based on available information. It is only an advisory opinion and should not be construed as binding on any individual or as expressing an absolute standard of medical practice. Medical opinion may vary regarding the appropriateness of a particular treatment or service in a given situation. Differences in an individual case should be reviewed by physician medical advisors. Differences of opinion between a medical advisor and attending physician should be referred to the county medical society where the physician practices.

Clinical Review

Superior Sagittal Sinus Thrombosis

Still a Killer

CATHRINA L. SCHELL, MD, MLS, *Acton, Massachusetts, and* RICHARD J. RATHE, MD, *Cheyenne, Wyoming*

Following treating a case of superior sagittal sinus thrombosis, we did an extensive search of the literature, eliciting 795 cases of the disorder. An analysis showed that even after the introduction of antibiotics, the preponderance of these cases have been diagnosed at autopsy. Our findings raise questions about the current methods of diagnosis and management of superior sagittal sinus thrombosis: Can the correct diagnosis be made earlier? Does a distinction between partial and complete thrombosis call for a different management?

(Schell CL, Rathe RJ: Superior sagittal sinus thrombosis—Still a killer. West J Med 1988 Sep; 149:304-307)

Superior sagittal sinus thrombosis is by no means a diagnosis of the past. In the preantibiotic era, mortality from the septic form of the disorder was 100%, and there has been little improvement in the outcome since the development of antibiotics.[1] The case we report prompted a thorough search of the literature, which elicited no comprehensive literature review of superior sagittal sinus thrombosis. In 1986 Southwick and co-workers reviewed only septic causes of dural thrombosis in the antibiotic era.[1] They cite 23 cases of the septic form of superior sagittal sinus thrombosis.[1] We found 795 cases of the disorder. An analysis of them offers insight into the effects of diagnostic timing, treatment type, and the extent of thrombosis on mortality. A clinical suspicion of the diagnosis is essential to an early recognition and survival, as our case report shows and other published accounts verify.

Report of a Case

The patient, a 33-year-old obese woman, was seen in the emergency department after two witnessed grand mal seizures. Her chief complaint was headache that was diffuse and throbbing. Despite medication, it had become progressively worse to the intensity of a "bomb" over the previous three days. She refused to uncover her eyes, and her neck was too painful to move.

She had felt well until a "cold" three months before being seen, from which she had not recovered when her vision became blurred. An ophthalmologist discovered posterior uveitis with visual deficit, and pars planitis was diagnosed. A systemic evaluation showed no abnormalities, laboratory values were normal, and a test for antinuclear antibody was negative. Prednisone therapy was started. A follow-up examination six weeks later revealed that her vision and uveitis had improved and her disc margins were sharp. Three days later she called another physician because she had severe headache not alleviated by taking aspirin. He prescribed orphenadrine citrate (Norgesic Forte) 24 hours before her arrival in the emergency department postictal.

Her medical history includes a tubal ligation; a right nephrectomy for kidney stones in a partial, nonfunctioning, horseshoe kidney; sinusitis; a recently normal Pap smear; and no previous history of headaches. One of five brothers died at age 21 of cerebral hemorrhage. Her mother is alive and well in her 80s, and her father died of alcoholism. She said she did not use tobacco, alcohol, or other recreational drugs. A review of systems elicited diplopia for the past two days and sudden neck immobility for 24 hours.

On physical examination her temperature was 37°C (98.6°F), her pulse rate was 72 per minute, respirations 16, blood pressure 120/78 mm of mercury, weight 83 kg (184 lb), and height 1.5 m (5 ft). She appeared in a toxic state but was alert and oriented to person, place, and time. Her facial veins were distended over the entire face, and she had pronounced photophobia. Her extraocular movements were intact without nystagmus. Her pupils were small and equally sluggish; disc margins were blurred but still definable, and the visual fields were full. Examining her teeth revealed mostly caries. Her neck was exquisitely tender to light touch, and the patient could not move her neck in any direction. The abdominal examination elicited no abnormalities except for a visible nephrectomy scar. On neurological examination she was right-handed, her memory was intact, and her speech was clear. Reflexes were symmetric and 3+. She had pronounced withdrawal on Babinski's and Chaddock's testing, but on Bing testing, both toes were downgoing. The cranial nerves were intact, as were coordination, sensation, muscle tone, and strength.

She was admitted to hospital to rule out meningitis. A lumbar puncture done immediately showed an opening pressure of more than 550 mm of water, no leukocytes, 5 erythrocytes, a glucose level of 74 mg per dl, and a protein level of 60 mg per dl. Ink and Gram's stains were negative. Further analyzing the cerebrospinal fluid showed a herpes simplex virus type 1 titer of 1:512 and an Epstein-Barr virus titer of 1:160. No virus was identified in cultures. She had a leukocyte count of 17,000 per μl with a leftward shift. A glucose level and electrolyte values were normal. A computed tomographic (CT) scan was done and a neurologist consulted. Although the CT scan was initially interpreted as normal, the

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
IV = intravenous

neurologist questioned an empty δ sign. Digital subtraction angiography was done, which clearly showed total thrombosis of the superior sagittal sinus (Figure 1). A regimen of intravenous (IV) dexamethasone, mannitol, ampicillin, and gentamicin sulfate was started.

Hospital Course

An infectious diseases consultation revealed that one week before admission, the patient had picked at a comedo on her nose, a common source of infection leading to intracranial sinus thrombosis. Her antibiotic regimen was changed to IV oxacillin sodium when a few staphylococci grew from a nares culture. Within three days, the patient began having less eye and head pain. She gradually began to move her neck and removed the towel covering her eyes. Her therapy was tapered from IV dexamethasone to oral prednisone, with the administration of oxacillin continued. Asymptomatic, she was discharged 14 days after admission on a regimen of prednisone, phenytoin sodium, and aspirin.

Ten days later she limped into the office with left calf pain. A venogram confirmed the presence of deep venous thrombosis. She was then admitted for anticoagulation therapy, and a hematologic evaluation showed no abnormalities. Tests for human leukocyte antigen B5 and C1-esterase inhibitor were negative. A month after being discharged on a regimen of warfarin sodium and phenytoin, she had difficulty urinating, so went to an emergency department where she was given trimethoprim and sulfamethoxazole for a presumed urinary tract infection. The following day she came into the office bleeding at the gums and complaining of no urine production. Catheterizing with a straight catheter returned only overt blood. A serum creatinine level was 3.7 mg per dl; it had been normal on previous admissions. Her prothrombin time was more than 60 seconds.

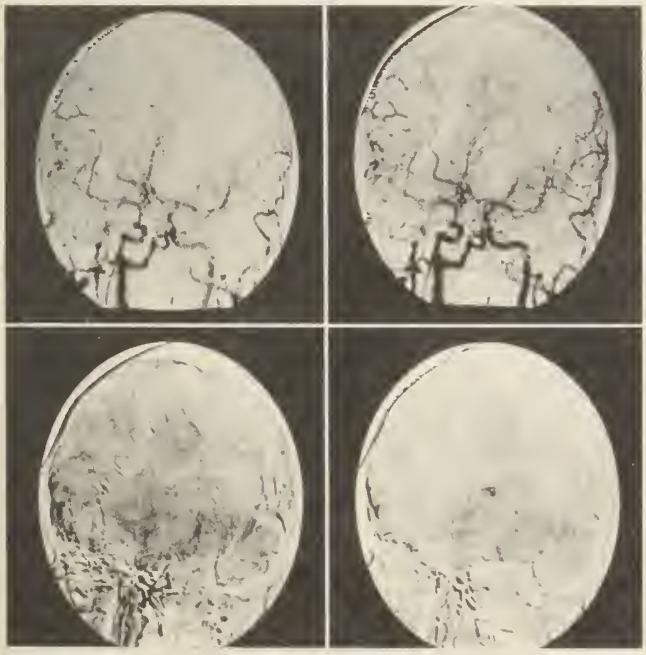

Figure 1.—A digital subtraction angiogram (**top photos,** arterial phase; **bottom photos,** venous phase) shows complete thrombosis of the superior sagittal sinus.

She was admitted for the third time in three months. A renal ultrasonogram showed an enlarged left kidney without evidence of hydronephrosis, a retrograde ureterogram showed no obstruction, and a nuclear medicine study showed findings consistent with renal vein thrombosis. The patient was then given a bolus of 250,000 units of streptokinase through a peripheral vein followed by 100,000 units an hour for 3½ hours when she began to excrete blood-tinged urine. The streptokinase therapy was then stopped and the administration of heparin started. The patient excreted 1,300 ml of urine over the next 24 hours after being anuric for almost 48 hours. At this point, she was transferred for expert consultation. A workup that included tests for protein S, protein C, and antithrombin III elicited no abnormalities, and she has remained stable on a regimen of warfarin and phenytoin for more than a year.

Summary

Despite three separate sites of thrombosis, this patient had normal values on a hematologic workup. She had no

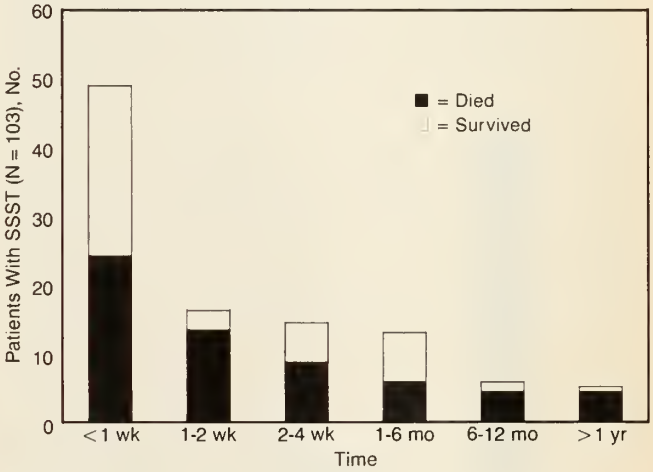

Figure 2.—The graph shows the effects of diagnostic timing on survival in patients with superior sagittal sinus thrombosis (SSST).

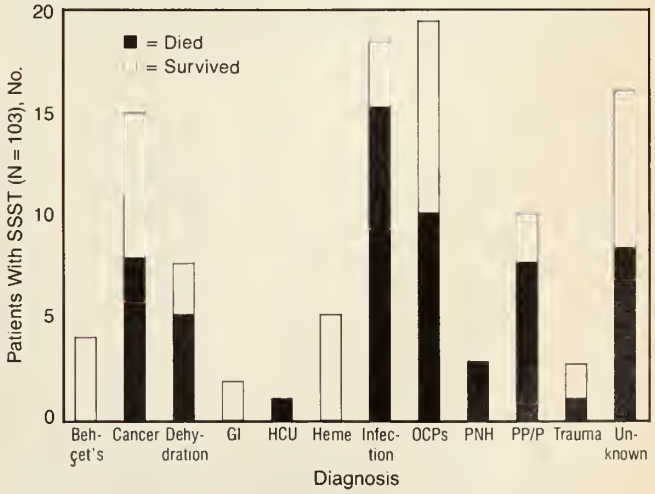

Figure 3.—The graph shows the outcome of patients with superior sagittal sinus thrombosis (SSST) caused by various disorders. GI = gastrointestinal, HCU = homocystinuria, Heme = hematologic disorders, OCPs = oral contraceptives, PNH = paroxysmal nocturnal hemoglobinuria, PP/P = postpartum and pregnancy-related disorders.

evidence of the nephrotic syndrome, which causes an acquired antithrombin III deficiency. Carcinoma, another source of hypercoagulability, has been repeatedly looked for in this patient and not found. Behçet's disease may present as dural sinus thrombosis, and uveitis is common in such cases.[2] The patient had both of these as well as sedimentation rates between 39 and 90 mm per hour. Thus far she lacks ulcers necessary for a diagnosis of Behçet's disease. Her history leads one to suspect an infectious cause, but with uveitis and elevated sedimentation rates, Behçet's disease is a consideration that may yet unfold.

Discussion

An extensive literature search found 2,055 references on intracranial sinus thrombosis. Of the 795 cases of superior sagittal sinus thrombosis, only 103 from 67 different articles were described fully enough for comparison.[2-68] The results of the literature analysis are summarized in Figures 2 through 5. Of 103 cases, 50% were diagnosed at autopsy, while the mortality was 56%. The ratio of women to men was 2:1. The mean age at the time of diagnosis was 27 years. The most common symptom was severe headache (53%), followed by seizures (49%); hemiplegia, quadriplegia, or paresis (48%); coma (38%); visual disturbances (25%); and nuchal rigidity (18%). Common signs were an elevated cerebrospinal fluid pressure (46%)—in most cases being more than 200 mm of water—coma (38%), and papilledema (33%).

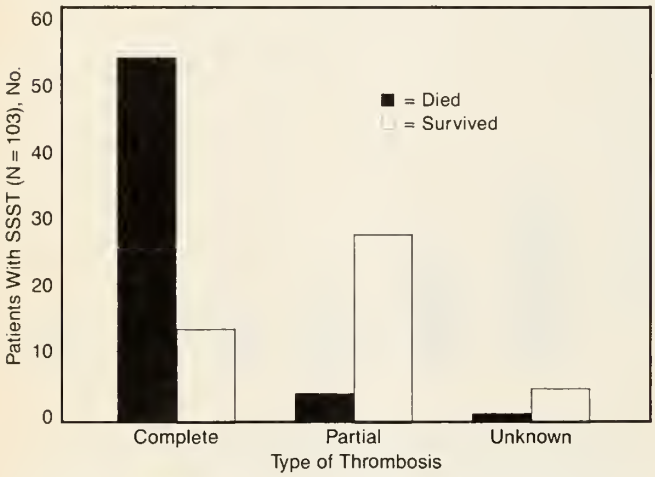

Figure 4.—The graph shows the mortality of superior sagittal sinus thrombosis (SSST) by extent of thrombosis at the time of diagnosis.

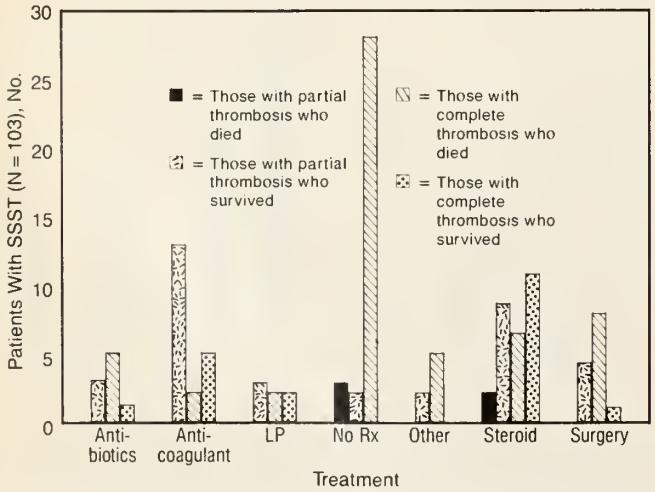

Figure 5.—The graph shows the results of various treatments for superior sagittal sinus thrombosis (SSST). LP = lumbar puncture, Rx = treatment.

These findings add little to existing descriptions of superior sagittal sinus thrombosis, but the results of the literature analysis provide some new perspectives of import to clinicians:

- The literature indicates a better outcome with earlier diagnosis and treatment (Figure 2).
- Patients with certain disorders causing superior sagittal sinus thrombosis, like Behçet's disease, had a consistently better outcome (Figure 3).
- The extent of thrombosis may be a key to survival; to our knowledge, no investigation has been done of this.

At the time of diagnosis, 31 of 103 patients had partial intracranial sinus thrombosis and 66 had complete (total occlusion) thrombosis. Only four patients with partial thrombosis at the time of diagnosis died.[6,54,56,68] On the other hand, only 14 with complete thrombosis at the time of diagnosis survived (Figure 4). Two patients with partial thrombosis survived without treatment,[4,54] but no one having complete thrombosis survived without treatment. Partial thrombosis resulted in death with no treatment or when giving steroids was the sole therapy, while patients with complete thrombosis fared better with the use of steroids only or in combination with anticoagulants (Figure 5).

Just as completed stroke calls for a different management, so it may be with superior sagittal sinus thrombosis. Di Rocco and colleagues reported excellent results with the use of urokinase and heparin, but all of their cases were diagnosed within four days of symptoms, and at the time of diagnosis all had partial thrombosis.[19] The question is whether their success was more from the treatment modality than from a quick diagnosis or the presence of only partial thrombosis. In general, 103 cases are too few for concrete conclusions, but they are enough to raise such questions to strengthen the base of investigation.

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Clinical Conference

Arsenic Poisoning

Discussant
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This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of New Mexico School of Medicine, Albuquerque. Taken from a transcription, it has been edited by Ralph C. Williams, Jr, MD, Professor and Chair of the Department of Medicine.

MICHAEL S. GORBY, MD*: This generation of clinicians is relatively unaware of the hazards of arsenicals. Advances in the treatment of syphilis and parasitism—which primarily used arsenicals—and in industrial and environmental public health have dramatically decreased clinicians' exposure to cases of arsenic toxicity. Unfortunately, the problem is still present, and it would be a mistake to assume it no longer exists. Arsenic is still the most common source of acute heavy metal or metalloid poisoning and is second only to lead with respect to chronic ingestion.[1] I have been involved in the care of two patients with arsenic poisoning in a span of eight months while at the Albuquerque Veterans Administration Medical Center. One was a fulminant and fatal case of acute poisoning after a disturbed 17-year-old woman intentionally ingested an arsenic trioxide-containing rodenticide. The other is a case of chronic arsenic poisoning from an as-yet-unidentified source resulting in several hospital admissions and many medical complications in a 64-year-old man. The clinical material presented herein is from the records of these two patients.

To understand arsenic in biology, one must first understand its chemistry. Arsenic is a member of the nitrogen family or group 5(a) of the periodic table of the elements. It has atomic number 33 with an atomic weight of 74.9 and is classified as a transition element or metalloid. This classification reflects the fact that arsenic commonly forms complexes with metals, but it also reacts readily to form covalent bonds with carbon, hydrogen, and oxygen. In fact, far more organic compounds of arsenic have been made than of any other trace element.[2] Arsenic may exist in three different oxidation or valence states, namely, the metalloid (0 oxidation state), arsenite (trivalent or +3 oxidation state), and arsenate (pentavalent or +5 oxidation state). Different arsenic-containing compounds vary substantially in their toxicity to mammals. Arsine gas (AsH_3) is clearly the most toxic, followed in order of generally decreasing toxicity by inorganic trivalent compounds, organic trivalent compounds, inorganic pentavalent compounds, organic pentavalent compounds, and, finally, elemental arsenic. Some arsenic compounds are apparently not toxic at any dose.[2] Toxicity also depends on other factors such as physical state—gas, solution, or powder—particle size, the rate of absorption into cells, the rate of elimination, the presence of impurities, and the nature of chemical substituents in the compound. Arsenicals are not cumulative in most mammals, and toxicity parallels excretion.[3] Arsine toxicity has been thoroughly reviewed, is associated with a unique and rapid hemolysis not occurring in other types of arsenic poisoning, and will not be discussed further in this review.[4]

Because of the complex chemistry of arsenic, it is difficult to discuss arsenic poisoning as a single clinical disorder. Critically evaluating published work on this topic is also hampered when it is not made clear what specific chemical compounds are discussed. The use of the blanket term, arsenic, is inappropriate. In this review I will concentrate on delineating the intriguing and important role this element has played throughout history and on the varied ways one may be exposed to arsenic. Brief discussions of the toxicity and biochemistry of arsenic and the clinical manifestations and treatment of arsenic poisoning will follow. Interested readers are referred to several excellent reviews on these matters.[3,5,6]

Sources of Exposure

Exposure to arsenic may come from natural sources, from industrial sources, or from intentionally administered sources, with either a benevolent or a malevolent intent.

Natural Sources

Arsenic is ubiquitously distributed in the environment. Sea water ordinarily contains 0.006 to 0.03 parts per million (ppm) of arsenic.[7] It is the 20th most common element in the earth's crust, although its concentration varies greatly.[8] In active geothermal areas, arsenic is naturally present in soil in amounts as high as 20 ppm, and levels of several hundred ppm may be found after years of spraying with pesticides.[9] Arsenic is present in all living organisms. The average daily human intake is 0.5 to 1 mg, most of which is in the form of food and water.[3] The highest concentrations are found in fish and crustaceans, and urinary arsenic concentrations can increase tenfold after a large seafood meal. The normal body burden in adults is approximately 20 mg.

Environmental arsenic mainly exists as sulfide complexes such as realgar (As_2S_2), or orpiment (As_2S_3) and iron pyrites (FeAsS) and is only occasionally found in its pure elemental

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state. The Arabic word for orpiment—a corruption of *auri pigmentum,* meaning "king's gold"—was *Az-zernikh,* and it is the probable root word of the present term. Arsenic ores are usually found in large concentrations in the presence of other metal ores, many of which are sought commercially. When heated to 193°C (379°F), arsenic sublimes from ores and oxidizes readily to trivalent As_2O_3. This is a fine granular white powder and is known as white arsenic, arsenic trioxide, or, for centuries, as simply arsenic. The ancients obtained "arsenic" in this manner by roasting arsenical ores in air and collecting the volatilized arsenic as arsenic trioxide. Therefore, human exposure to arsenic trioxide began with the first primitive smelter.[10]

Industrial Sources

Humans in their use of natural resources release arsenic into the air, water, and soil. Anthropogenic sources exceed natural sources by at least threefold in terms of quantities of arsenic released into the environment. Moreover, these sources are geographically confined and may present local environmental hazards. The main sources of anthropogenic arsenic release into the environment are through the smelters of the metal industry, fertilizer and pesticide spraying, and the burning of fossil fuels.[7]

Arsenical compounds have found use as the active ingredients in a number of commercial products. They are or have been used in wood preservatives, pesticides, herbicides, fungicides, cattle and sheep dips, desiccants, defoliants, dyestuffs, feed additives, drugs, and war gases. A number of miscellaneous uses include those such as a glass clarifier, an important element in the electronics industry, and as an additive that increases hardening and heat resistance of metal alloys. The use of arsenic in many of these areas followed the development of the industrial revolution as a consequence of being an inexpensive by-product of the smelting of nonferrous metals such as copper, iron, zinc, gold, and other metals. Arsenic's commercial uses peaked in the late 1960s and have been steadily declining in most areas. Exceptions to this decline are the use of arsenic in the electronics industry and as a wood preservative in conjunction with copper and chromium. Although arsenicals remain the best agents for certain applications in agriculture, their usage in insecticides and herbicides has largely been replaced by hydrocarbon products. Today less than 30,000 tons of arsenic trioxide is manufactured secondarily in world production.[11] About 97% of the arsenic produced enters end-product manufacture in the form of white arsenic, the remaining 3% as metal for metallurgic additives. The only United States plant recovering arsenic from metal ores is a copper smelter in Tacoma, Washington. Present US markets for arsenic trioxide are shown in Figure 1.

Occupational and environmental health problems can result from the ubiquitous commercial presence of arsenicals. To paraphrase the title of a well-known play, this may be a problem of "arsenic and old waste." The National Institute of Occupational Safety and Health estimates that 1½ million people are potentially exposed to arsenic during the course of their work.[12] Smelter workers appear to have an increased mortality—primarily from lung cancer—proportional to their arsenic exposure.[13] Large-scale accidental arsenic poisonings have occurred in the past. At the turn of this century, more than 6,000 British beer drinkers were apparently poisoned with arsenic in the well-known "Staffordshire beer epidemic." This was a manufacturing mishap in the Manchester area of England traced primarily to arsenic in iron pyrites used to make sulphuric acid that, in turn, was used to make the glucose for brewing. Although some have incriminated selenium in this epidemic, it provided the impetus for the first government-mandated industrial regulations for arsenic.[2] In 1955 more than 12,000 Japanese infants were poisoned, causing 130 deaths, when the sodium phosphate used as a stabilizer in infant formula preparations was found to be contaminated with arsenic.[7] More recently, 11 cases of arsenic poisoning in a western Minnesota community were attributed to the consumption of well water contaminated from an adjacent arsenical insecticide storage dump.[9] There is also a report of probable arsenic poisoning of a family in rural Wisconsin from extensive burning of marine plywood—treated with chromium-copper-arsenate—in a poorly ventilated cabin.[14]

Administered Sources

Arsenic has been used as a medicine and as a poison since humans first became interested in chemistry.

Malevolent intent. Arsenic probably has the worst public relations record of any element, and its name has become almost synonymous with the term poison. The popularity of arsenic as a poison is due more to its availability, inexpensiveness, and the fact that it is tasteless and odorless than to its extreme toxicity. Common arsenicals simply are not that efficient as a poison, leading to a slow and painful, not instantaneous, death. In his play *Arsenic and Old Lace,* John Kesselring was careful to include cyanide and strychnine in the concoction with which the little old ladies swiftly and unerringly dispatched their gentleman callers. Arsenic simply would not have done it alone, yet it made a far more intriguing title.

Aristotle and Socrates had known a few vegetable poisons such as hemlock and henbane. They were most familiar, however, with the inorganic poison arsenic trioxide that, in

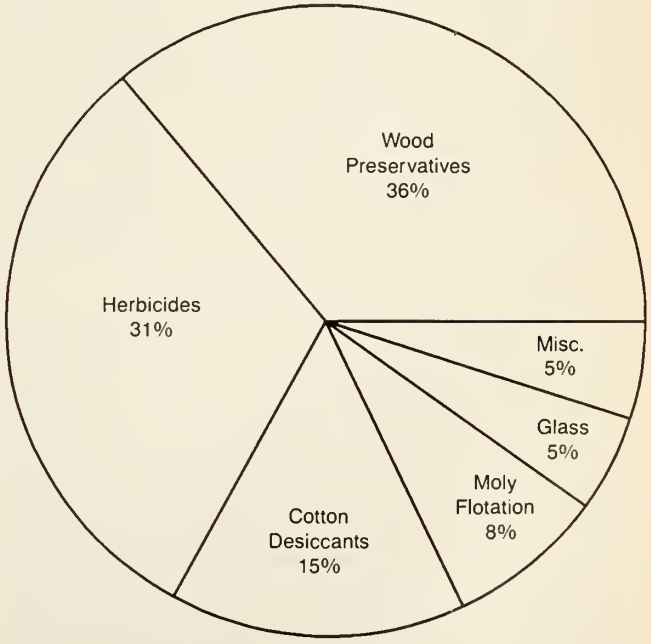

Figure 1.—The figure shows the United States markets for arsenic trioxide estimated by the American Smelting and Refining Company.[11]

TABLE 1.—*Poisoning Attempts in 19th Century France per 1,000**

Arsenic	331	Opiates	12
Phosphorus	301	Mercurials	9
Copper	183	Antimonials	6
Mineral acids	54	Cyanides	5
Cantharides	35	Iron	5
Strychnine	14	Other	45

*Reported in 1885 by Blyth.[16]

the course of the following centuries, became the poison of poisons. One of the earliest documented cases of arsenic poisoning was Nero's poisoning of Britannicus to secure his Roman throne in the year 55 AD. The poisoner became an integral part of social and political life in the early Middle Ages—arsenic was known to be the favorite of some. The records of the city councils of Florence and Venice contain ample testimony of the political use of poisons. Contracts were recorded, naming victims and prices, and when the deed was accomplished, the notation "factum" would be entered into the city archives.[15] Poisoners like the Borgia pope, Alexander VI, and his son, Cesare Borgia, became legendary, as did such sinister figures as Teofania di Adamo and Marie Madeleine, who in the 17th century killed left and right with arsenic solutions. White arsenic acquired so terrible a reputation that ultimately it was called *poudre de succession,* "inheritance powder." Arsenic was the favorite poison of 19th century France, as recorded by early forensic toxicologists (Table 1).[16] A French woman named Catherine Deshayes commercialized this service, which grew to infamous proportions, earning her the title, "La Vosine." Her business dissolved with her execution when a special judicial commission established by Louis XIV convicted her of many poisonings, including more than 2,000 infant victims.[15]

Poisoning seems to have been accepted as one of the normal hazards of daily life in this era. Devices and methods of poisoning proliferated at an alarming rate. Arsenic's popularity as a poison, however, declined dramatically in the latter half of the 19th century, at least partly due to the development of a highly reliable and sensitive assay for arsenic described by Marsh in 1836.[17] The importance of this test can be appreciated from its use as decisive evidence in the trial of a celebrated poisoner, Marie Lafarge, for the murder of her husband in 1842.[17] Variations of this test that involve acidifying body tissue or fluids and detecting liberated arsine gas colorimetrically are still in use today as qualitative diagnostic tests (Reinsch's test, Gutzeit's test).

Two rather notable case histories of arsenic exposure with malevolent intent have appeared in the scientific literature recently. These cases illustrate some of the power and pitfalls of the forensic toxicology of arsenic. The first is that of Charles Francis Hall, a Cincinnati printer and businessman who, at the age of 37, felt a messianic calling to explore the North Pole. He left family, home, and business and became one the of the best and most daring of Arctic explorers. In 1871 he headed the US North Polar Expedition and pushed his ship, Polaris, through ice-choked seas to the very northern tip of Greenland and planned to winter there. The crew had other ideas. They were hostile and afraid, but Hall ignored them, making frequent solo sojourns into the surrounding vastness. He returned one night, in the darkness and cold, drank a cup of black coffee, and became violently ill, experiencing a seizure. He rallied, lived for two weeks, then died and was buried in a two-foot deep grave in the permafrost. Nearly a century later, adventuresome researchers located the grave and did an autopsy that included neutron activation analysis of fingernails and hair samples.[18] This revealed "an intake of considerable amounts of arsenic by C. F. Hall in the last two weeks of his life."

A second case involves an interesting debate in the scientific and popular literature on how to account for elevated concentrations of arsenic in specimens of hair preserved from the scalp of Napoleon Bonaparte, who died in 1821. Theories to explain these arsenic levels abound and include the work of secret assassins, long-term ingestion by the deposed emperor in the paranoid belief it would protect him from attempted poisonings, and administered therapies for illness. The best accepted explanation appears to be that it came from his wallpaper! The green copper arsenite pigments (Scheele's green and Paris green) were introduced in about 1780 and were soon widely used in paints and wallpapers. On damp wallpaper, many molds can metabolize arsenic compounds to volatile, poisonous trimethylarsine, which is released into the air in the room. Throughout the 19th century, many people were made ill or even killed in this manner.[19] When researchers analyzed an original sample of wallpaper from Napoleon's residence on Saint Helena, they found enough arsenic to be capable of causing illness but probably not death.[20]

Benevolent intent. The medicinal effects of arsenicals were written about by Hippocrates (460-357 BC), Aristotle (384-322 BC), and Pliny the Elder (23-79 AD). Hippocrates had administered orpiment and realgar as escharotics and as remedies for ulcers. Paracelsus (1493-1541), one of the strangest and most paradoxic characters in medical history, is known to have used elemental arsenic and mercury extensively. He formulated many then-revolutionary views that remain an integral part of the structure of toxicology. He promoted a focus on "the toxicon," the toxic agent, as a chemical entity. A pertinent remark attributed to Paracelsus is that "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy."[15] Small doses of inorganic arsenicals have long been felt to have a "tonic" or "alterative" property, which led to their enthusiastic use for more than two centuries. Initially these compounds cause a cutaneous capillary flush, giving a "milk and roses" complexion enjoyed by many women. Local mountaineers in Austria, the so-called arsenic eaters, have consumed large quantities of arsenical ores in the belief it improves endurance at high altitudes, increases weight, strength, and appetite, and clears the complexion.[10] Taken internally in either liquid or solid form, injected hypodermically, inhaled as a vapor, administered intravenously, and, on rare occasions, even given in enemas, arsenic proved to be one of the mainstays of the 19th century *materia medica.*[21] Many arsenic-containing "medicinals"—Fowler's solution, Asiatic pills, Donovan's solution, DeValagin's elixir, to name but a few—came into use for a variety of ailments. These were considered at various times specific therapy for anorexia and other nutritional disturbances, neuralgia, rheumatism, asthma, chorea, tuberculosis, diabetes, intermittent fever, skin disorders, and hematologic abnormalities. Perhaps the most widely prescribed of these agents was Fowler's solution, a 1% potassium arsenite concoction introduced by Thomas Fowler in the London Pharmacopoeia in 1809. It

was withdrawn from the US market in the 1950s after several case series linking its prolonged use to skin changes, cutaneous malignant lesions, and neuropathies appeared. Arsenic retains its mystique as a panacea in many cultures. At the popular hot springs in Ojo Caliente, New Mexico, visitors receive a pamphlet, "The Doorway to Better Health," attesting to the benefits of using arsenic. It reads, "To achieve the best results, it is suggested to drink the pleasant tasting waters, as well as to bathe in them. . . . The *arsenic* water is the only known water of its kind in this country. Arsenic is a most powerful healing element."

By the early 1900s, physicians began using the less toxic organic preparations of arsenic—sodium cacodylate and sodium arsanilate—for the treatment of pellagra, as well as for malaria and sleeping sickness. In 1909, Ehrlich's experiments with arsenic led to the widespread use of arsphenamine (salvarsan), often called "606," which, until its replacement by penicillin, was the principal drug in the treament of syphilis for nearly 40 years. Its success stimulated intense activity on the part of the organic chemists who extended the list of synthesized arsenic compounds from 606 to an estimated 32,000.[3] Arsenicals in medicine are now largely replaced by antibiotics but are still used as antiparasitic agents in veterinary medicine and occasionally in patients with trypanosomiasis and amebiasis.

Toxicity and Biochemistry

Much of the basis of our current understanding of the mechanism of arsenic toxicity in living systems comes from work on arsenic toxicity in animals in the late 1800s, from the development of organic arsenical drugs during the early 1900s, and from work stimulated during the 1940s by the need to find effective antidotes for arsenical warfare agents. The difference in toxicity between trivalent and pentavalent arsenic compounds can best be understood by considering the biochemical mechanism of action of these two distinct families of compounds. Present knowledge concerning the biochemical mechanisms of arsenic toxicity in mammals is far from complete, although some aspects of this problem have been studied in considerable detail. Single cell studies have established that specific forms of arsenic can be cytotoxic, and it is generally thought that the overt toxicity of arsenic is due to the inhibition of critical sulfhydryl-containing enzymes by trivalent arsenic.[6] Many enzymes are susceptible to deactivation by arsenic. In most cases the enzyme activity can be restored by adding an excess of a monothiol such as glutathione, suggesting that the inhibition is due to the reaction of the arsenic with a single sulfhydryl group in the enzyme molecule. An important exception to this generalization, however, proved to be the pyruvate oxidase system, which could not be protected against trivalent arsenicals by even a 200% excess of monothiol. Such an apparent anomaly was clarified when it was shown that arsenicals can complex with two sulfhydryl groups in the same protein molecule, thereby forming a stable ring structure that is not easily ruptured by monothiols. This finding stimulated the testing of various dithiol compounds for their ability to block the action of arsenicals on pyruvate oxidase and led to the discovery of 2,3-dimercaptopropanol, also known as British antilewisite. This agent eventually became a widely used antidote for arsenic poisoning, allowing the formation of a stable, soluble five-membered ring that is excreted in the urine (Figure 2).

The simultaneous interaction of arsenic with two thiol groups led Peters to postulate the existence of a dithiol-containing cofactor in the pyruvate oxidase system.[22] This idea was later verified with the identification of lipoic acid. The pyruvate oxidase complex is necessary for oxidative decarboxylation of pyruvate to acetyl coenzyme A and carbon dioxide before it enters the tricarboxylic acid cycle. This enzyme system comprises several enzymes and cofactors. In the presence of trivalent arsenic, a dihydrolipoyl-arsenite chelate is formed, preventing the reoxidation of the dihydrolipoyl group necessary for continued enzymatic activity, and this pivotal enzyme step is shut down.[23] It is also apparent that some cellular effects of thiamine deficiency are identical to arsenic poisoning and may explain their similar clinical manifestations (Figure 3).[24]

These well-defined cellular effects of trivalent arsenic may be modified in more complex systems by in vivo oxidation-reduction reactions, differences in uptake and loss from particular organ systems, and by differences in the natural susceptibility of various tissues. Little is known about the biotransformation of arsenicals in humans. Some pentavalent compounds are partly reduced in vivo to the more toxic trivalent forms, but the redox equilibrium in vivo favors the pentavalent state.[6] Although pentavalent arsenic does not appear to lead to enzyme inhibition, it cannot be dismissed as nontoxic because of its potential to uncouple oxidative phosphorylation. The mechanism is thought to be related to the competitive substitution of arsenate for phosphate, with which it is isoelectric and isosteric, with the subsequent formation of an unstable arsenate ester bond that is rapidly hydrolized. Thus, the so-called high-energy bonds of adenosine triphosphate are not conserved in the presence of arsenate.[3] This process is termed arsenolysis. Arsenic may therefore be doubly toxic to cells by inhibiting energy-linked

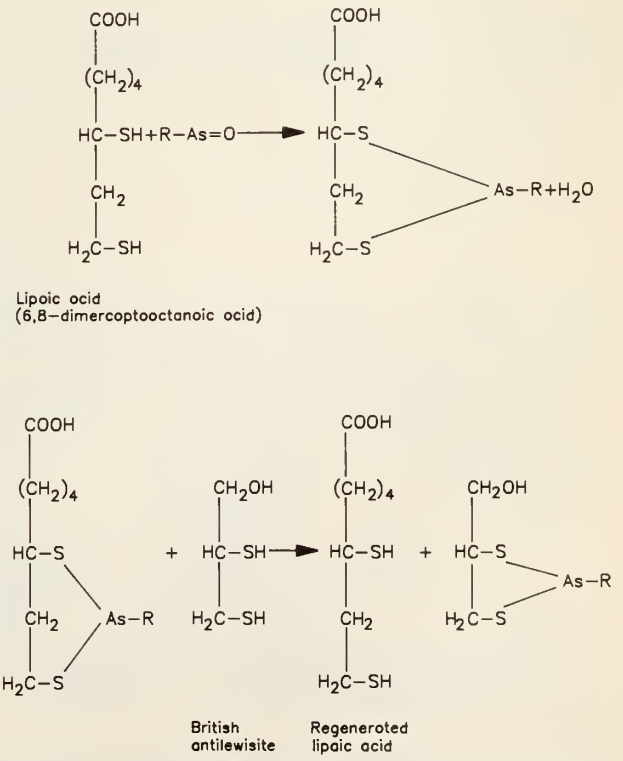

Figure 2.—Lipoic acid reacts with a trivalent monosubstituted arsenical and is regenerated by adding British antilewisite.

functions of the mitochondria in two very different ways. Trivalent arsenic inhibits the reduction of nicotinamide adenine dinucleotide by deactivating critical enzymes in the tricarboxylic acid cycle, and pentavalent arsenic uncouples oxidative phosphorylation by arsenolysis.

Soluble forms of arsenic are nearly completely absorbed from the gastrointestinal or respiratory tract and probably also from the skin. Excretion is primarily through the urine in the form of methylated arsenic, although the organic arsenic in seafood is largely excreted unchanged.[25] Absorbed arsenic is initially bound to the protein portion of hemoglobin, yet leaves the intravascular space within 24 hours and is concentrated in the liver, kidneys, spleen, lungs, and gastrointestinal tract. After two to four weeks, most arsenic remaining in the body is found in hair, nails, and skin due to the high sulfhydryl content of keratin and is slowly excreted in this manner. Renal dysfunction is a major impediment to the normal excretion of all arsenic compounds.

Clinical Manifestations

The clinical manifestations of arsenic poisoning depend on the type of arsenical involved and on the time-dose relationship of exposure. A fatal dose of arsenic trioxide is probably in the 200- to 300-mg range, yet a dose of 20 mg has been life-threatening, and recovery from 10 grams has occurred.[5] Clinical manifestations may conveniently, although somewhat artificially, be described as either acute or chronic (Table 2).

Acute Poisoning

Symptoms of acute intoxication usually occur within 30 minutes of exposure. Initially a patient may have a metallic taste or notice a slight garlicky odor to the breath, associated with a dry mouth and dysphagia. Severe nausea and vomiting, colicky abdominal pain, and profuse diarrhea with rice-water stools abruptly ensue. In acute arsenic poisoning of massive proportions, almost always as an attempt at suicide, the fundamental lesion of endothelial cellular toxicity can be considered to account for the predominant clinical features. Capillary damage leads to generalized vasodilation, transudation of plasma, and shock. Arsenic's effect on the mucosal vascular supply, not a direct corrosive action, leads to transudation of fluid into the bowel lumen, mucosal vesical formation, and sloughing of tissue fragments. Cyanosis, hypoxic encephalopathy and seizures, acute tubular necrosis, and death may occur due to hypovolemia.

TABLE 2.—*Clinicopathologic Findings in Acute and Chronic Arsenic Poisoning*

System	*Acute*	*Chronic*
Skin	Hair: delayed loss; nails: Mees's lines (2-3 weeks postingestion)	Melanosis, Bowen's disease, facial edema, hyperkeratosis, cutaneous cancers, hyperpigmentation
Neurologic	Hyperpyrexia, convulsions, tremor, coma	Encephalopathy, polyneuropathy, tremor, axonal degeneration
Gastrointestinal tract	Abdominal pain, dysphagia, vomiting, bloody or rice-water diarrhea, mucosal erosions	Nausea, vomiting, diarrhea; anorexia, weight loss
Liver	Fatty infiltration	Hepatomegaly, jaundice, cirrhosis
Kidney	Tubular and glomerular damage—oliguria, uremia	Nephritic findings
Hematologic		Bone marrow hypoplasia; anemia, leukopenia, thrombocytopenia; impaired folate metabolism; basophilic stippling and karyorrhexis
Cardiac	ST-T wave abnormalities, prolonged QT interval, ventricular fibrillation, atypical ventricular tachycardia	...

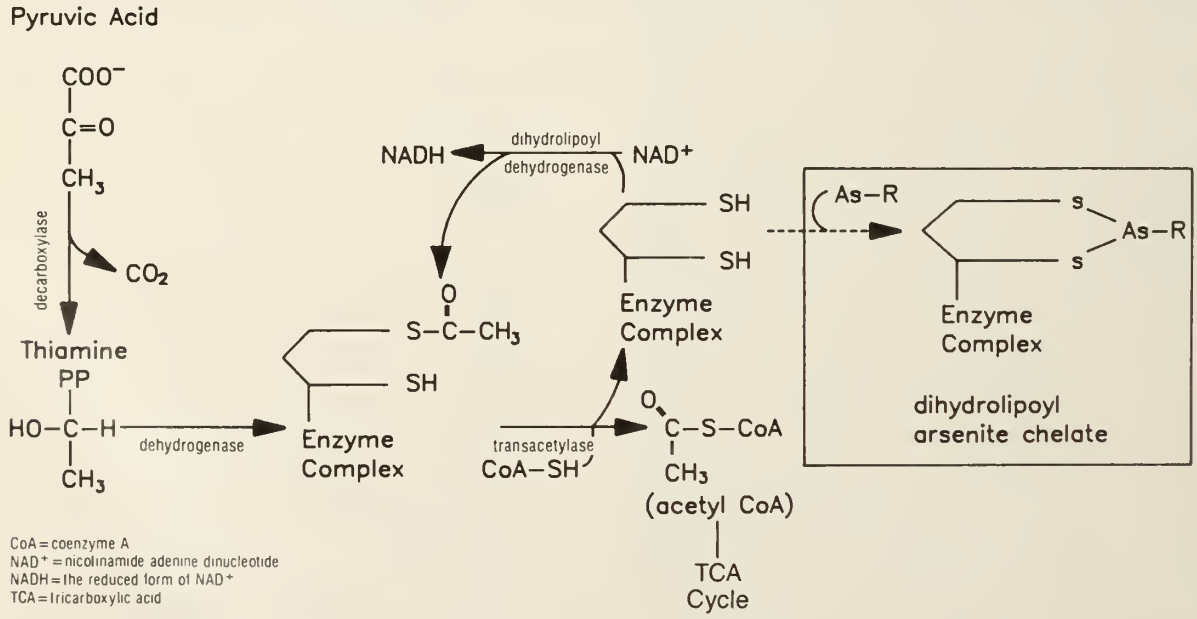

Figure 3.—The effect of trivalent arsenic on sulfhydryl enzyme systems: Shown here is the inhibition of pyruvate oxidase by the formation of an arsenite chelate preventing reoxidation of the dihydrolipoyl group necessary for continued enzymatic activity. Succinate oxidation is disrupted in an identical manner, as are many other enzymes.

Following the gastrointestinal phase, multisystem organ damage may occur. If death does not occur in the first few hours from irreversible circulatory insufficiency, it may result from hepatic or renal failure over the next several days. Cardiac manifestations include acute cardiomyopathy, subendocardial hemorrhages, and electrocardiographic changes. The most common changes on an electrocardiogram are prolonged QT intervals and nonspecific ST-segment changes.[26] A case of an atypical ventricular fibrillation resembling torsades de pointes has been reported.[27] The pathologic lesions described in patients with rapidly fatal arsenic intoxication are fatty degeneration of the liver (Figure 4), hyperemia and hemorrhages of intestine (Figure 5), renal tubular necrosis, and demyelination of peripheral nerves.

Chronic Poisoning

Chronic arsenic poisoning is much more insidious in nature, often with multiple hospital admissions before the correct diagnosis is made. The source of arsenic exposure is discovered in less than 50% of cases. There are several good reviews of arsenic's effects on various organ systems.[3,10] I will mention only briefly the most prominent chronic manifestations involving the skin, blood, and neurologic systems.

The cutaneous changes are characteristic yet nonspecific.

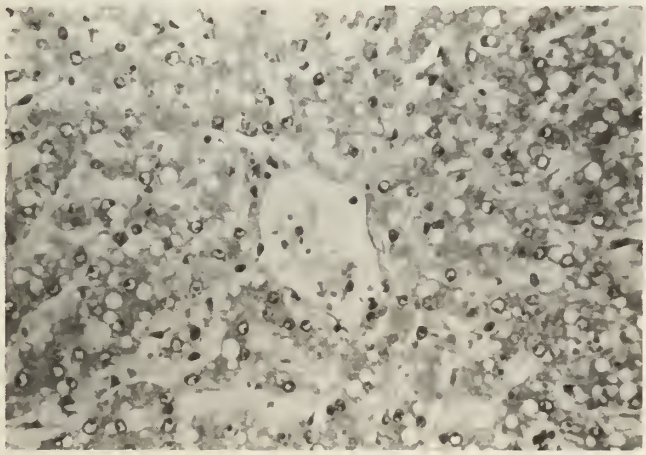

Figure 4.—The photomicrograph of liver shows acute fatty change from a patient dying 12 days after a massive (more than 7 grams) overdose of arsenic trioxide (original magnification × 40).

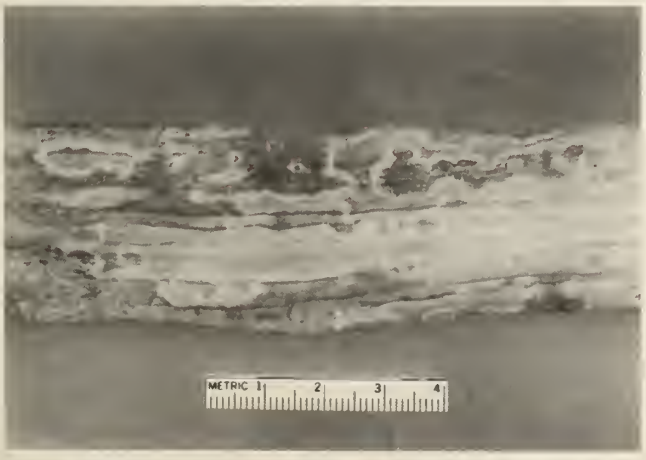

Figure 5.—The photograph shows the gross specimen of distal esophagus from the same patient as in Figure 4. Necrotic oral lesions and pronounced hemorrhagic gastritis were also noted.

An initial persistent erythematous flush slowly leads to melanosis, hyperkeratosis, and desquamation. The skin pigmentation is patchy and has been given the poetic description of "raindrops on a dusty road." The hyperkeratosis is frequently punctate and occurs on the distal extremities. A diffuse desquamation of the palms and soles is also seen. Long-term cutaneous complications include the development of Bowen's disease and multiple cutaneous malignant tumors.[28] Brittle nails, patchy alopecia, and facial edema can occur. Transverse white bands across the nails (Aldrich-Mees's lines) are frequently seen three to four weeks after an acute exposure and may even be used to date the event.

Anemia and leukopenia are almost universal with chronic arsenic exposure; thrombocytopenia frequently occurs. The anemia is usually normochromic and normocytic and caused at least partially by hemolysis.[29] Interference with folate metabolism and DNA synthesis may result in megaloblastic changes.[30] Karyorrhexis, an accelerated pyknosis of the normoblast nucleus, is characteristic of arsenic poisoning. This is manifested as bizarre nuclear forms seen on bone marrow examination (Figure 6). Basophilic stippling is also seen. Aplastic anemia progressing to acute myelogenous leukemia has been reported.[31]

A peripheral neuropathy is the hallmark of chronic arsenic poisoning but may be seen within two hours of ingestion. Usually it is a symmetric polyneuropathy of both sensory and motor nerve fibers, often resembling the Landry-Guillain-Barré syndrome in its presentation.[32] On microscopic examination, there are resorption of myelin and destruction of axonal cylinders progressing to nerve atrophy and perineural fibrosis (Figure 7).

Treatment of Arsenic Poisoning

In patients with acute arsenic poisoning, supportive therapy and chelation treatment are indicated. Essential supportive measures, as with any poisoning, include scrupulous intestinal decontamination—charcoal lavage and the administration of cathartics—and adequate intravenous fluid therapy. Exchange transfusions may be of help in clearing the blood of elevated arsenic concentrations early in the course. Hemodialysis may be a useful adjunct in treating a patient with acute arsenic poisoning with concomitant renal failure.[33]

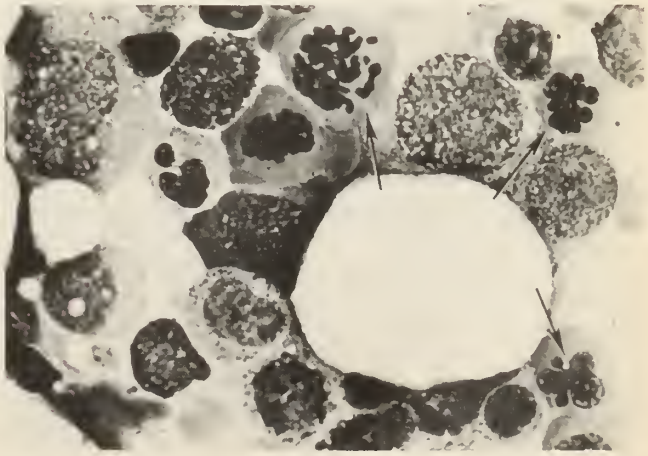

Figure 6.—The photomicrograph is of a bone marrow specimen from a 64-year-old man with chronic arsenic poisoning. Most notable are bizarre nuclei in the erythrocytic precursors—karyorrhexis—indicated by arrows (original magnification × 100).

Figure 7.—The photomicrographs of osmium-stained sections of sural nerves show **(A)** a normal specimen taken at autopsy and **(B)** a surgical specimen from the same patient as in Figure 6. A loss of the myelin sheath—normally stained by osmium—and perineural fibrosis can be seen (original magnification × 20).

Dimercaprol (2,3-dimercaptopropanol) is the traditional chelating agent used, but penicillamine has been used with some success.[34] Parenteral dimercaprol is administered intramuscularly at the initial dose of 3 to 5 mg per kg of body weight every four hours. The dose should be tapered but administration continued until the urinary arsenic excretion is less than 50 μg per 24 hours. This therapy is frequently effective in preventing or neutralizing systemic toxicity. In most cases the degree of recovery from neuropathy, aplastic anemia, encephalopathy, and jaundice is limited and directly related to the initial severity of the systemic involvement and the rapidity with which chelation therapy is initiated. Penicillamine, although only a monothiol agent, has been used successfully with the great advantage that it may be orally administered. Both agents have a high frequency of side effects, although this is less of a problem in the presence of large amounts of body arsenic. A recently reintroduced drug that appears to be a promising agent for treating arsenic poisoning is 2,3-dimercaptosuccinic acid. This is a dithiol agent, can be orally administered, and has few reported side effects.[35] Experience, however, is limited with the use of this drug.

Chronic arsenic poisoning can also be treated with chelating agents, but the possible benefits must be weighed against the known side effects. There is little convincing evidence of the benefit of chelation therapy in most cases of chronic poisoning.

Summary

Arsenic is a metalloid that has played an important and fascinating role throughout recorded history. Exposure to toxic amounts of arsenic continues to occur in this country. Certain aspects of the metabolism and biochemistry of the arsenical compounds are now well understood, and the application of this knowledge has led to a rational basis of therapy for cases of acute poisoning. The clinical manifestations of arsenic poisoning are myriad, and the correct diagnosis depends largely on being aware of the problem.

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Urgency Incontinence in Children

STRESS INCONTINENCE IS NOT AN ENTITY WE GENERALLY RECOGNIZE IN THE PEDIATRIC POPULATION. Stress incontinence is incontinence with laughing, coughing, or lifting, and that's usually something we think of in older persons—the multiparous woman; the man with some prostatism or after prostatic surgery.

What we usually see in children is urgency incontinence, and that's entirely different. That's these uninhibited bladder contractions. There is a group of patients, generally adolescent girls, who have "giggle" incontinence. "Giggle" incontinence is one of the biggest pains in pediatric urology because it is untreatable. It is absolutely untreatable. These girls will be in a school situation with their friends, and you know how young girls are. They'll start talking, and suddenly someone will say "BOO," and they'll all explode in laughter . . . and one girl explodes from both ends. She's just sitting in a puddle of urine, and it's very embarrassing.

I've tried using an anti-cholinergic. I've tried exercises. I've sent some of them to the behavior-modification people at Johns Hopkins who are interested in this. In my youth, I even operated on one of these children, which I will never do again. It's untreatable. All you can do is try to get them to change their laugh pattern. And it's also unexplainable to me. I really do not understand what happens with "giggle" incontinence, but the only thing I suggest to them is, make sure that, before they stand in the corner with their girlfriends, they go to the toilet. At least if they're going to lose their urine, they'll lose less. Also, they should try not to explode with laughter. Well, you know, you hate to see a young girl not being able to giggle. That's a real problem.

—A. BARRY BELMAN, MD

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Medical Staff Conference

Liver Transplantation—The First 25 Years

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

RICHARD K. ROOT, MD*: *Liver transplantation has recently moved from the realm of experimental therapy to that of effective therapy for certain forms of hepatic failure. This Medical Staff Conference, which brings us up to date with advances in this area, has been organized by Nancy L. Ascher, MD, Director of the Liver Transplant Program at UCSF, and her colleagues, John P. Roberts, MD, and John R. Lake, MD.*

NANCY L. ASCHER, MD, PhD†: This year marks the 25th anniversary of clinical liver transplantation; Thomas Starzl, MD, performed the first human liver transplant in 1963.[1] Although this sparked worldwide interest in the field, long-term survival was not attained until 1967.[2] Early one-year survival rates were poor, about 30%, until 1980 when cyclosporine was introduced as the principal immunosuppressive agent.[3] Using cyclosporine—as well as technical advances and improved patient management—ushered in survival rates of 65% from 1980 to 1984[3]; currently many centers report one-year survival rates of 80% or better.[4-6] After a 1983 National Institutes of Health consensus conference concluded that liver transplantation had become a therapeutic modality,[7] many states and private insurers began to pay for this procedure. Activity in the field has also increased from 26 transplants done in 1981 to more than 950 in the United States in 1987.

This review is intended to update readers on advances in this field, and we will attempt to provide insights into the striking increase in survival following liver transplantation. Readers must understand, however, that there have been few randomized trials concerning any aspect of clinical liver transplantation. Comparisons of patient selection, different surgical techniques, or immunosuppressive regimens depend on historical controls, comparisons between different centers using different techniques, animal studies, and local prejudice. Therefore, the validity is questionable.

Patient Selection

Careful selection of potential recipients and improved preoperative management have contributed to the improved transplant results. The selection process should be designed to answer three important questions: First, does the patient have a liver disease that is soon to progress to death or that significantly impairs the patient's quality of life and for which no alternative therapy exists? Second, are there medical contraindications present that would likely preclude a successful liver transplant? Finally, does the patient have the psychosocial characteristics necessary to comply with a postoperative immunosuppression protocol?

Appropriate indications for liver transplantation can be divided into general indications applicable to most forms of chronic liver disease and specific indications appropriate to one or only a few diseases (diseases for which liver transplantation has been done are listed in Table 1).[8-10] Indications for liver transplant that are applicable to most chronic liver diseases include ascites refractory to medical management, encephalopathy that significantly impairs life-style, variceal hemorrhage that is refractory to sclerotherapy, and the hepatorenal syndrome. Indications that apply to specific liver diseases include refractory pruritus (chronic cholestatic disorders such as primary biliary cirrhosis or extrahepatic biliary atresia), severe metabolic bone diseases with fracture (primary biliary cirrhosis),[11] recurrent cholangitis (primary sclerosing cholangitis or extrahepatic biliary atresia), neurotoxicity (Wilson's disease), and correction of metabolic diseases related to impaired synthesis of a liver-specific protein (familial hypercholesterolemia, tyrosinemia, α_1-antitrypsin deficiency, hereditary hyperoxaluria, the Crigler-Najjar syndrome type II).

Although these indications for liver transplantation are generally accepted, the decision regarding the exact timing of the operation is made difficult by the varying natural history of the liver disease.[8] Ideally, transplantation should be done at a time when a patient's general medical condition would minimize operative mortality and morbidity,[12,13] but where the liver disease severely jeopardizes one-year survival. Natural history data guide this decision. For example, patients with primary biliary cirrhosis may remain relatively free of complications until serum bilirubin levels exceed 10 mg per dl[14,15]; at that point, complications can be anticipated and a liver transplant should be considered. Similarly, in patients with fulminant liver disease, a prothrombin time of longer than 20 seconds or stage III encephalopathy (or both) indicate limited survival without transplantation.[16,17] Unfortunately, the natural histories of diseases such as chronic active hepatitis with cirrhosis or primary sclerosing cholangitis are much less predictable; consequently, decisions regarding the timing of transplantation are more difficult.

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ABBREVIATIONS USED IN TEXT

CMV = cytomegalovirus
HBsAg = hepatitis B surface antigen
HIV = human immunodeficiency virus

The contraindications for liver transplantation have evolved as the field has developed. Widely accepted contraindications include sepsis, extrahepatic malignancy, and advanced cardiopulmonary disease—such as an arterial oxygen pressure of less than 55 torr or pulmonary hypertension.[9,10] Many transplant centers regard a positive test for the human immunodeficiency virus (HIV) as a contraindication based on data showing that in HIV-positive patients who have undergone transplantation (before the availability of HIV testing), the acquired immunodeficiency syndrome often develops shortly after immunosuppressive therapy is instituted.[18]

Relative contraindications to liver transplantation include the presence of the hepatitis B surface antigen (HBsAg), hepatobiliary malignancy, portal vein thrombosis or other anatomic anomalies, a previous portacaval shunt operation, advanced age, renal failure, and active infection, although some centers pursue transplantation in these groups. Past experience indicates that the vast majority of HBsAg-positive patients retain or redevelop evidence of active viral replication after liver transplantation. Whether active or passive immunization protocols will affect this remains to be proved.[19,20] In addition, the incidence and natural history of recurrent hepatitis B virus disease in the graft are not yet defined. Primary hepatobiliary malignancy—that is, hepatocellular carcinoma and cholangiocarcinoma—is becoming a less frequent indication for liver transplantation due to the high incidence of tumor recurrence and poor long-term survival (20% survival at three years).[8,21] The fibrolamellar variant of hepatocellular carcinoma[22] and incidental tumors in children are exceptions. Experience with patients with portal vein thrombosis or a previous portacaval anastomosis indicates that these patients can successfully undergo a transplant operation, although often at the risk of increased perioperative blood loss. These cases require appropriate angiographic definition of the anatomy and careful preoperative planning. Elderly patients must be carefully examined for disease in other organ systems.[23] Patients with concomitant renal failure may require simultaneous renal transplantation.

TABLE 1.—*Diseases for Which Liver Transplantation Has Been Done*

Adults	*Children*
Cirrhosis	Cirrhosis
Primary biliary cirrhosis	Biliary atresia
Chronic active hepatitis	Chronic active hepatitis
Cryptogenic cirrhosis	Cryptogenic cirrhosis
Secondary biliary cirrhosis	Caroli's disease
Primary sclerosing cholangitis	Congenital Hepatic Fibrosis
Alcoholic cirrhosis	Metabolic Disorder
Fulminant Liver Disease	α_1-Antitrypsin deficiency
Viral	Wilson's disease
Drug-induced	Tyrosinemia
Toxin—such as *Amanita* mushroom sp	Glycogen storage disease
Metabolic Liver Disease	Byler's disease
Wilson's disease	Sea-blue histiocytosis syndrome
Hemochromatosis	Galactosemia
Protoporphyria	Protoporphyria
Hereditary oxalosis	Familial hypercholesterolemia
Hepatic Vein Occlusion	Hepatobiliary Malignancy
Veno-occlusive Disease	Hepatoblastoma
Hepatocellular carcinoma	Hepatocellular carcinoma
Cholangiocarcinoma	
Angiosarcoma	

Assessing a patient's compliance is difficult and varies with the experience and philosophy of the transplant program. Factors associated with poor compliance with immunosuppression regimens include active alcohol or other drug abuse, active psychiatric illness, or a history of poor compliance with medical treatments. For patients in whom compliance is an issue, a thorough psychological evaluation by trained professionals is mandatory.

Because decisions regarding the indications, timing, and appropriateness of liver transplantation are complex, most programs use a selection committee to assist in patient-selection decisions.[24] Selection committees typically comprise representatives from the departments of surgery, medicine, pediatrics, anesthesiology, intensive care, social work, pathology, psychiatry, nursing, and hospital administration. At the UCSF Medical Center, patient-selection committee meetings are monitored by a member of the lay public, and records of the proceedings of the meetings are maintained as a matter of public record.

Donor Selection

Currently there is a shortage of donors, particularly in the pediatric age group. At present, 30% of children who are acceptable candidates for transplantation die while waiting for a suitable donor liver.[25] With this shortage, it is important that all physicians be aware of the need for donation and approach the families of potential donors with the consideration of organ donation. In doing so, they may expect that the families will consent, as it has been estimated that more than 80% of families may choose to donate the organs of a relative if given this option.[26,27]

The main criteria for selecting a donor are ABO blood-type compatibility (for stable recipients), the relative body size match, and the physiologic state of the donor. Although the organ from a person with blood type O (universal donor) can be used in any blood-type recipient, this practice should be avoided except for recipients who are deteriorating rapidly. This is to allow type O recipients the same chance to receive a liver as the frequency of the blood type in the general population because type O recipients can receive livers only from blood type O donors. Furthermore, there is a suggestion that the use of nonidentical but compatible blood group transplants may be associated with decreased survival.[28] In cases of dire need, ABO-incompatible donors may be used (primarily in type O recipients). Although this is associated with decreased survival, it is not clear whether the poorer survival results from selecting patients who are more gravely ill or from crossing the ABO barrier—resulting in increased rejection or requiring increased immunosuppression. At the University of Minnesota (Minneapolis) Medical Center, ten liver transplants from blood group A donors to group O recipients were done with a 70% one-year actuarial survival. All these transplants were carried out in patients with an urgent need for transplantation (N. L. Ascher, MD; J. P. Roberts, MD; and J. R. Lake, MD, unpublished data, July 1988). Splenectomy, antilymphocyte globulin, and ex-

change transfusions for rising anti-A titers in the first week following transplant were used prophylactically.

Donor-recipient size match is also important. Using a liver that is too large can lead to respiratory compromise and pressure necrosis of the graft. Using a donor liver that is too small may result in a mismatch of vessel size with a resultant relative stenosis. A recent advance in obtaining organs for pediatric patients is the partial resection of larger livers to fit into smaller recipients.[29]

One of the most dreaded outcomes of liver transplantation is primary nonfunction where the donor organ fails from the outset to produce coagulation factors or bile. Primary nonfunction is commonly fatal without immediate retransplantation. To avoid this catastrophe, an accurate assessment of the potential function of the donor liver is important. Tests that offer sufficient predictive power to allow discriminating between donor organs are currently lacking,[30] although work is progressing in this area.[31] A sensitive and specific method of predicting graft function may increase the pool of available donors, as many donor organs considered clinically unsuitable may actually provide good function after a transplant.

Current absolute contraindications to donation are a positive antibody to HIV, the presence of HBsAg, systemic malignancy, or sepsis.

Preserving the Donor Organ

Until recently, donor livers were preserved in a high osmolar, potassium-rich solution initially used for renal preservation. The mechanism of action of these solutions appears related to the impermeant solutes that maintain a relatively normal state of hydration of cells during preservation.[32] A new solution with a different set of impermeant substances—hetastarch, melitose (raffinose), and lactobionate—will likely extend the maximal preservation time from 10 hours to at least 20 hours.[33] Longer preservation times will create the possibility of intracontinental sharing, superior recipient preparation, and an unhurried approach to the transplant procedure. Extended preservation may allow local teams to procure a liver and ship it to a transplant center via scheduled flights. This would end the expensive use of chartered aircraft to transport donor livers.

Organ Sharing

In October 1987, a nationwide organ sharing system was instituted.[34] The system is structured so that possibly available organs are first offered to local programs. If no local recipient is available, then the organ is offered to centers within a defined geographic region. If no regional recipient is available, the organs are then offered nationally. The selection of recipients is based on criteria that allow for the level of care the recipients are requiring. Patients in an intensive care setting are assigned the highest priority. Patients who are still able to work are assigned the lowest priority.

Operative Technique

Orthotopic liver transplantation remains a surgical tour de force. Every aspect of the operation is fraught with potential complications. Much of the improved survival following liver transplantation can be related to improvements in the surgical and anesthetic techniques. The operation consists of three phases: mobilization of the recipient liver, the anhepatic phase during which the vessels are clamped while the recipient liver is removed and the donor liver sewn in, and the period following revascularization of the donor liver.

The operative challenge of liver transplantation can be traced to two specific complications of chronic liver disease. First, there is impaired hemostasis from diminished hepatic synthesis of coagulation factors and thrombocytopenia resulting from portal hypertension with hypersplenism. Second, portal hypertension also produces increased venous collaterals, which are often most severe when there are adhesions and scars from previous operations. The combination of large nests of vessels to divide and the lack of coagulation factors and platelets to provide hemostasis leads to the possibility of extensive blood loss. The technical problems of recipient hepatectomy are compounded in patients with previous right upper quadrant operations. If patients are possible transplant candidates, a right upper quadrant procedure should be deferred, particularly central portosystemic shunts.

The anesthetic management is directed toward maintaining an adequate intravascular volume and a functioning hemostatic system. This requires supplementing clotting factors with fresh frozen plasma and cryoprecipitate and correcting thrombocytopenia. Anesthesiologists also must be able to administer large volumes of blood and blood products rapidly. The development of the rapid transfusion device has allowed for the delivery of warmed blood at a rate greater than 2 liters per minute.[35] A third anesthetic problem is maintaining a normal electrolyte balance. Hypocalcemia from receiving large volumes of citrated blood, acidosis, and hyperkalemia from reperfusion of the donor organ and from the banked blood are common intraoperative events.

Venovenous Bypass

When liver transplantation was first attempted in animals, it was found that normal dogs did not tolerate prolonged clamping of the portal vein and inferior vena cava. Hemodynamic instability led to the development of a method of shunting the blood from the portal vein and inferior vena cava to the superior vena cava (venovenous bypass).[36] This provided the hemodynamic stability necessary to complete the operation. Later work showed that bypass was not necessary in dogs that had preexisting portal hypertension. Many humans also tolerated vessel clamping without the use of the bypass. In liver transplantation, clamping of the portal vein and infrahepatic vena cava has three undesirable effects: a loss of preload from a decreased venous return, an increase in the vena caval pressure that theoretically can impede renal venous return and compromise renal function, and bowel edema from obstructing the portal system. Because of these problems, the Pittsburgh group reinstated the use of the bypass, first in heparinized patients (which led to excessive bleeding), then in those who had not received heparin.[37] The incidence of renal dysfunction and blood loss was diminished in their patients with the use of the bypass as compared with historical controls.

Other groups have reported successful liver transplantation without using a bypass and without an increase in renal dysfunction or blood loss.[4,38] It is possible to overcome the loss of preload and maintain good urinary output during the anhepatic phase without bypass by using the rapid transfusion device. Advocates of the bypass describe the major ben-

efit as allowing for an extended anhepatic phase when training surgeons or in difficult technical situations.[39]

The use of the bypass is not without risk. Pulmonary embolism, nerve injury, lymphoceles, and wound infections have all been reported as complications. The specific benefits of the bypass are unclear and would have to be determined in a randomized trial.

Biliary Reconstruction

The biliary drainage procedure is responsible for most of the complications following liver transplantation. In early reports of liver transplantation, an incidence of 34% to 53% and a mortality of 25% to 30% occurred from biliary tract complications.[40,41] The incidence of biliary complications has decreased to 12% to 13%.[42,43] Improvements have come from standardizing the reconstruction of the biliary tract to either a choledochocholedochostomy—donor bile duct to recipient bile duct—in recipients with normal bile ducts or a Roux-en-Y choledochojejunostomy in those patients with abnormal bile ducts, such as patients with extrahepatic biliary atresia or sclerosing cholangitis.

Biliary complications require immediate intervention to divert the bile, usually done by transhepatic biliary drainage and drainage of any associated bile collections. A disruption of the anastomosis requires revision while late strictures may be managed by balloon dilatation and stenting. Two caveats have been suggested in cases of biliary complications. The first is that ultrasonography may be unreliable in diagnosing biliary tract dilatation in a liver transplant recipient,[44] and, second, the presence of biliary tract problems should raise the possibility of a hepatic artery thrombosis.[45]

Hepatic artery thrombosis. Because liver transplantation interrupts the arterial collaterals to the liver, subsequent thrombosis of the hepatic artery results in a total loss of arterial blood flow to the hepatic parenchyma and the biliary tree, leading to hepatic necrosis and biliary complications. The resulting biliary tract lesion resembles sclerosing cholangitis with bile duct strictures and dilatation. The incidence of hepatic thrombosis is about 3% to 10%, with a higher rate in pediatric patients and in patients with complex vascular reconstructions.[46] Hepatic artery thrombosis occurring immediately after transplant is particularly hazardous as new collaterals have not developed; the mortality in this setting is 50%. Current emphasis has been on early detection by the use of electromagnetic flow probes to recognize decreased flow in the hepatic artery,[47] the use of Doppler ultrasound to test for arterial patency in the postoperative period, and the use of aspirin to prevent thrombosis.

Thrombosis in the immediate postoperative period usually requires retransplantation, although it is possible that early recognition, a thrombectomy, and an anastomotic revision may preserve the liver and biliary tree.[48] Late thrombosis may lead to abscess formation and biliary strictures or follow a more benign course, possibly due to the development of collaterals to the liver.

Portal vein thrombosis. Thrombosis of the portal vein occurs in 1.8% of transplants and carries a better prognosis than hepatic artery thrombosis. Liver function may be maintained, but portal hypertension and variceal hemorrhage frequently develop. The Pittsburgh group currently recommends conventional treatment for varices in those patients who have normal liver function following portal vein thrombosis.[49]

Nonsurgical Complications in the Immediate Postoperative Period

Renal dysfunction is common in the posttransplant period. Some series report the need for dialysis in 25% of patients after a transplant.[50] Immediate renal dysfunction in liver transplant recipients is often related to the use of cyclosporine. Acute cyclosporine toxicity is mediated by a reduction of renal blood flow and the glomerular filtration rate.[51] This action is manifested clinically by oliguria accompanied by a low fractional excretion of sodium. This can result in significant salt and water retention despite the presence of hypervolemia and a salt and water excess due to intraoperative crystalloid and colloid use. Our approach to this problem is to administer intravenous cyclosporine continuously beginning at a dose of 0.25 mg per kg body weight per 24 hours, with a gradual increase in the dose to a maximum of 3 mg per kg per 24 hours. To overcome the renal salt retention, intravenous furosemide and dopamine hydrochloride are administered to maintain a good urine output, euvolemia, and a return to near the preoperative weight within 72 hours. If the urinary output remains low, the cyclosporine therapy is discontinued for four hours and reinstituted at a lower dose when the urinary output returns to normal. This approach has led to an incidence of posttransplant dialysis of less than 5% at the University of Minnesota and UCSF.[4] The use of lower doses of cyclosporine is possible because of the concomitant use of azathioprine in the postoperative period.

Infection

Infectious complications are common with the use of immunosuppression. It is estimated that, on average, at least one episode of bacterial infection will develop in a patient with a liver transplant, and there is a 40% to 50% chance that fungal or viral infections will develop.[52]

The sources of bacterial infections are generally the biliary tree, intra-abdominal abscess, pneumonia, and central venous catheters.[4] These infections are often associated with complications of the liver transplant; the result of decreasing technical complications should be a decrease in the number of bacterial infections.

Pneumocystis carinii pneumonia is an important problem in transplant patients. These infections can be eliminated in immunocompromised patients through the prophylactic use of trimethoprim and sulfamethoxazole.[53] Intermittent therapy—three times a week—has recently been shown to be as effective as daily therapy in decreasing fungal infections.[53] With prophylaxis, *P carinii* morbidity and mortality should be eliminated in transplant patients.[54]

Viral Infections

Viruses of the herpes family are the most common viral pathogens following a transplant. Herpes simplex and varicella-zoster virus infections generally present with mucocutaneous manifestations, and therapy with acyclovir appears to be effective. More serious infections occur with the cytomegalovirus (CMV). The onset of CMV infection generally occurs within the first two months. In one report, 9 of 12 patients in whom CMV infection developed were symptomatic.[55] The infections that appear to be particularly serious are those in patients with negative CMV serologic tests before transplant (primary infections). These patients appear to acquire the infection from either a seropositive liver donor or blood donors. The ability to protect seronegative recipi-

ents from primary infection appears to be possible through the use of seronegative liver and blood donors, but the availability of large amounts of CMV-negative blood products is limited. Using the new antiviral agent ganciclovir has been reported to be effective in serious CMV infections following liver transplantation.[56]

Mechanisms of Liver Transplant Rejection

The incidence of liver transplant rejection ranges from 20% to 80% depending on the criteria used to make the diagnosis. Some groups require only histologic evidence of rejection while other groups require histologic changes in association with clinical manifestations or laboratory abnormalities or both. The classic histologic features of liver transplant rejection are primarily seen in the portal triads.[57,58] Portal-based cellular infiltrate, bile duct epithelial damage, and central vein and portal vein endotheliitis are the most common features of rejection. The sites and distribution of the human leukocyte antigens within the liver correlate with the histologic picture of rejection and are felt to be of importance in the pathogenesis of rejection. Bile duct epithelium and central vein endothelium are rich in class I and class II antigens, and increased antigenic expression can be noted during acute rejection.[59] Hepatocytes have modest amounts of class I expression and virtually no class II expression even during acute rejection. This may explain why hepatocyte injury is seen only late in the rejection process.

An example of the specificity of the rejection process for the portal tracts and particularly for the bile ducts is seen in the histologic features of the "vanishing bile duct" syndrome occasionally seen in cases of liver transplant rejection. In this variant of chronic rejection, an intense inflammatory reaction destroys the bile ducts, and after the bile ducts "vanish" the inflammatory cells also disappear, as if the bile duct epithelium were the only target of the inflammatory cells. The histologic finding following this rejection process is of hepatocytes that appear normal and portal tracts without inflammatory cells but also without bile ducts.[60]

A further refinement over identifying lymphocytes within the portal tract during rejection is the use of lymphocytic antigenic markers to identify specific lymphocyte subsets. Perkins and co-workers found that the patterns of T-helper cells alone or a combination of T-helper and T-cytotoxic/suppressor cells within the portal tracts predicted for and antedated clinical manifestations of rejection.[61] Thus, the current evidence supports a major cellular component in the rejection of liver allografts. The cellular rejection appears to be of the classic type, initiated by T-helper cells, which are stimulated by class II antigens in the bile duct epithelium and central vein endothelium, and effected through T-cytotoxic cells whose activity is directed against class I antigens present on bile duct epithelium, central vein endothelium, and less intensely on hepatocytes.

The role of antibodies in acute or chronic liver rejection is uncertain. The presence in a recipient of a preformed antibody against donor antigens does not adversely affect the liver allograft outcome.[62] The depletion of high antibody titer or inducer cells that amplify the antibody response can accompany the blood loss that frequently occurs during transplantation and may dampen the antibody's effect in graft injury.

A diagnosis of rejection based solely on histologic findings remains controversial. Until a randomized trial is carried out subjecting patients with histologic changes alone to either treatment or observation, the significance of histologic changes will remain unknown. Laboratory abnormalities, however, have been nonspecific in a number of studies; they do not differentiate rejection from other causes of hepatic dysfunction.[63] Clinical signs and symptoms of liver transplant rejection are equally nonspecific. Fever, a decreased bile output, a change in bile consistency, graft tenderness and swelling, increased ascites, and a decreased level of consciousness have all been reported to accompany rejection but are not specific. The group at the University of Minnesota reported on 58 consecutive patients who underwent weekly percutaneous biopsy after transplants to diagnose rejection. Treatment was instituted based on the histologic diagnosis of rejection. The incidence of biopsy-proved rejection was 77% in adult patients and 73% in pediatric patients. Moreover, with this aggressive approach, the incidence of patients requiring retransplantation for chronic rejection was less than 5%.[4] This compares favorably with a 20% to 25% retransplantation rate in other programs.[64] Moreover, despite the frequent need for the treatment of rejection, the death rate from infection following transplantation was only 11%.

Preventing Rejection

The agents used to prevent liver transplant rejection are the same ones used to maintain other whole-organ grafts. The current mainstay of immunosuppressive programs is cyclosporine, and most regimens involve combining two or more drugs to maximize immunosuppressive synergy and minimize drug toxicity. Cyclosporine, a cyclic endecapeptide first described by Borel and colleagues in 1977,[65] has profound inhibitory effects on interleukin-2 production and inhibits T-cell proliferation. This blocks amplification of the rejection reaction, dampening the full-blown rejection response. The side effects of cyclosporine use include nephrotoxicity, hypertension, hirsutism, hypertrichosis, gingival hyperplasia, malignancy, hand tremors, painful paresthesia of palms and soles, benign fibroadenomas, and hepatotoxicity. Many of these complications are dose related and can be resolved with dose modification.

Steroids continue as a major component of the antirejection regimen, acting at several levels of the immune response, including antigen processing and presentation, inhibition of lymphocyte proliferation, and decreased expression of class II antigens. The side effects of steroid use include sodium retention, hypertension, impaired wound healing, increased infections, and glucose intolerance. Azathioprine, an antimetabolite, inhibits cellular proliferation and is often used in conjunction with prednisone and cyclosporine. Its suppressive effects on the bone marrow can be titrated along with its dose.

Treating Rejection

The optimal therapy for liver transplant rejection has not been determined. According to the Boston Consortium Study, many first-time, mild rejection episodes can be successfully treated with increased doses of steroids. Continued rejection or subsequent rejections are best treated with antilymphocyte globulin or monoclonal OKT3 antibodies.[66] Administering these antilymphocyte preparations, though successful in treating rejection, is associated with an increased incidence of viral infections.[4]

Summary

Improved survival following liver transplantation in the 1980s has not been the result of any one advance. Earlier patient referral and better patient selection have led to recipients who are likely to be long-term survivors following a transplant while not eliminating those marginal patients who will benefit from it. Improvements in donor organ recovery have increased the pool of acceptable organs available and, therefore, have decreased waiting time, allowing transplantation before the irreversible deterioration of a recipient. Better operative techniques have led to fewer complications, and techniques of anesthetic management have decreased intraoperative death and postoperative morbidity. Immunosuppression and the treatment of rejection have improved, resulting in a decrease in retransplantation, making more organs available to other patients while not increasing the complications of immunosuppression.

These advances have occurred in an accelerated fashion since 1980. It would be expected that a plateau in improvements has not been reached yet, and the 1990s will herald not only improved survival but decreased costs, complications, and hospital stays.

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Epitomes

Important Advances in Clinical Medicine

Neurosurgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in neurosurgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Head Injury

THE CONSEQUENCES of minor and moderate head injuries have been the subject of ongoing controversy in the medical community for many years. Some have maintained that concussion is never associated with cognitive or behavioral sequelae, while others have argued that most patients suffering minor head injuries, and all with moderate head injuries, have at least transient cerebral dysfunction. Most recently, a series of objective studies has been carried out to detail both the short- and long-term consequences of head injuries that do not produce coma. Pioneering studies from New Zealand, followed by an important investigation at the University of Virginia, have suggested that minor and moderate head injuries can have long-term cognitive sequelae in a substantial number of patients.

It was recently shown that most patients who suffered a minor head injury, defined as a head injury producing a transient loss of consciousness and followed by a stay in hospital of no more than 48 hours, had evidence of transient cerebral dysfunction. Intellectual problems in the areas of memory, attention, and abstract thinking were seen on the initial evaluation within a week of injury. At one month, substantial improvement had occurred; at three months, the great majority of patients had returned to normal. About 15% continued to have significant cognitive sequelae, however. Behavioral manifestations such as headache, depression, insomnia, and imbalance or disequilibrium improved substantially in most patients at three months.

One can conclude from this multicenter study that minor head injury produces transient cerebral dysfunction, most of which is completely reversible and resolves within three months, but that there is a group of patients—"the miserable minority"—in whom long-term cognitive sequelae are present. In California alone, about 40,000 patients are admitted to hospital with minor and moderate head injuries each year. Many are dysfunctional for some months, either in the workplace or at home. Further delineation of this transient cerebral dysfunction and better treatment strategies for such patients are required.

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Timing of Surgical Therapy for Aneurysms

THE SUCCESSFUL TREATMENT of intracranial aneurysms remains a major challenge to the specialty of neurologic surgery. Although alternative forms of interventional neuroradiologic procedures are being developed, the time-honored definitive procedure of choice in the treatment of ruptured saccular intracranial aneurysms remains microsurgical exposure and clip obliteration of the lesion.

It is estimated that about 28,000 subarachnoid hemorrhages occur per year in North America and that a third of patients die as a result of their initial hemorrhage or are misdiagnosed. The other approximate two thirds of these patients reach facilities with neurosurgeons capable of definitively caring for the lesion but only half of this patient population has a reasonable outcome. The other half—an estimated 9,000 persons—die of the complications of rebleeding and vasospasm or medical and surgical complications.

The goal of surgical intervention is to prevent rebleeding and facilitate the treatment of vasospasm. Although "late" intervention still has its proponents, a more urgent and early approach may offer a more favorable outcome. Modern principles of neuroanesthesia, adjunctive measures to produce a "slack" brain—using mannitol and cerebrospinal fluid drainage—combined with microsurgical techniques, a judicious use of temporary clips, minimal brain retraction, and dissection within the subarachnoid cisterns and outside the brain offer the opportunity to successfully clip off the offending aneurysm from the adjacent circulation. This can be done soon after the hemorrhage, thus obviating the risk to the patient of rebleeding. Operating early also provides a surgeon the opportunity to open up the arachnoid cisternal pathways and evacuate some of the "toxic" subarachnoid blood and the potential for the topical administration of agents to counteract vasospasm. In the days following early surgical intervention, a patient can be safely managed with hypervolemic-hypertensive therapy should vasospasm become a clinical problem. Surgical treatment is not advisable in those patients in the midst of severe vasospasm, another compelling reason to intervene early.

From a technical standpoint, the surgical repair of aneurysms can now be done early. Although operating early has no direct result either favorable or unfavorable on the subsequent potential problem of vasospasm, it does effectively treat the rebleeding problem associated with these lesions.

An acute physician and public awareness of the "sentinel bleed" or early warning leak that so often seems to occur just before a full-blown aneurysmal rupture can lead to a greater accrual of early and accurately diagnosed patients in good clinical condition. By combining this effort with operating early, the incidence and the morbidity and mortality associated with rebleeding from ruptured intracranial aneurysms can be significantly reduced.

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Intravascular Detachable Balloon Embolization of Intracranial Aneurysms

THE CURRENT TREATMENT OF CHOICE for intracranial aneurysms is neurosurgical clipping. This procedure may be compromised due to the anatomic location, configuration, size, or calcification of an aneurysm. Detachable balloon occlusion may provide an alternative therapy for selected cases of difficult aneurysms.

Under fluoroscopic visualization, a silicone balloon is flow-directed through the intracranial circulation and guided directly into the aneurysm. Using real-time subtraction or "road mapping" techniques, the balloon is inflated with a hydrophilic polymer, hydroxyethyl methacrylate, which solidifies to create a permanent embolic agent. The balloon is then detached within the aneurysm, and angiography is done to confirm occlusion of the aneurysm with preservation of the parent artery. Ectatic aneurysms without a neck may be treated by occluding the aneurysm or the parent artery (or both).

The procedures are done from a transfemoral approach using local anesthesia to permit continuous neurologic monitoring of the patient's condition. The technique has been used to treat aneurysms of the proximal, mid, and distal basilar, posterior cerebral, lateral posterior choroidal, cavernous internal carotid, posterior communicating, carotid ophthalmic, carotid bifurcation, and middle cerebral arteries.

Because intravascular embolization of intracranial aneurysms is still a relatively new therapy and long-term follow-up is required, the patient selection criteria are conservative. Our series of more than 200 includes patients with aneurysms in which standard neurosurgical clipping techniques have failed, aneurysms in surgically inaccessible areas, or aneurysms associated with high surgical morbidity or mortality, or patients judged to be clinically unstable for general anesthesia and craniotomy.

The largest reported series has been from the Kiev Neurosurgical Institute, where 532 aneurysms have been treated with a mortality of approximately 7%. In this series only those patients not treatable by balloon occlusion were treated by craniotomy and clipping. It is hoped that advances in materials, techniques, and scientific exchange will continue to improve this developing technology.

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Indications for Cerebral Revascularization

CEREBRAL REVASCULARIZATION remains a viable treatment option for patients with cerebrovascular disorders. The International Cooperative Study of Extracranial-to-Intracranial Arterial Anastomoses helped to redefine and therefore limit the indications for these procedures and improved our understanding of cerebrovascular ischemia. An extracranial-to-intracranial (EC-IC) vascular anastomosis is clearly not efficacious in the treatment of patients with thromboembolic cerebrovascular disease. It is, however, a valid therapeutic option for a patient with the relatively rare recurrent transient ischemia from hypoperfusion that is refractory to optimal medical management.

The difficulty lies in deciding which patients suffer from cerebrovascular hypoperfusion and will therefore possibly benefit from revascularization of an ischemic vascular region. These patients must be studied and selected carefully. Attendant medical problems must be brought under optimal control. If patients remain symptomatic despite trials of aspirin and anticoagulants and they are reasonable candidates for an operation—from an anesthetic-risk perspective—then they may be considered for an EC-IC bypass procedure. Reproducible signs and symptoms of hemodynamic compromise must correlate with a demonstrable pathologic disorder on radiologic studies. Four-vessel head and neck angiography, including aortic arch views, is essential to document vascular occlusion or stenosis, the presence or absence of a collateral blood supply (or steal), and the location and caliber of extracranial vessels. Cerebral blood flow studies using stable xenon computed tomography with and without activation using acetazolamide (Diamox) have helped correlate ischemic symptoms with regions of relative hypoperfusion and limited autoregulatory reserve. Magnetic resonance (MR) imaging will reveal information about ischemia or infarction and is particularly useful when assessing posterior circulation vascular insufficiency. MR imaging will also document ventricular size and rule out other lesions, such as cyst, tumor, hematoma, or arteriovenous malformation, that might mimic ischemic cerebral disease.

EC-IC bypass remains an important adjunct in the treatment of patients with unclippable giant intracranial aneurysms. If hunterian ligation or an aneurysm-trapping proce-

dure is contemplated, a prophylactic EC-IC bypass to the appropriate vascular territory should be considered. Infective or traumatic intracranial aneurysms occasionally require excision (including a segment of the parent vessel). In these instances, an EC-IC bypass can maintain the viability of the tissue in the distal vascular bed of the sectioned parent vessel.

Deciding which procedure to do—anterior versus posterior circulation revascularization—is based on individual anatomic and pathologic factors, with the bypass directed at the ischemic region of greatest need. The techniques of these procedures have been well described. The formation of an anastomosis between the extracranial and intracranial circulation is a low-risk procedure, and long-term patency rates are high—90% to 98% in major studies. Venous interposition grafting has been described with good results but slightly lower patency rates—80% to 85%.

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Brain Tissue Transplantation

SINCE THE EARLY 1970s when neuroscientists began to describe the connections formed by fetal rat neurons transplanted to neonatal or adult rats, interest in the transplantation of mammalian neural tissue has been growing. Early experiments showed the potential of using fetal tissue transplantation techniques to study patterns of neuronal development, synaptic plasticity, and neural regeneration after injury. In the late 1970s, scientists in Scandinavia and the United States found that fetal dopaminergic neurons and adult adrenal medullary tissue could be transplanted to the brains of adult rats that had undergone nigrostriatal lesioning with 6-hydroxydopamine. Recipients of these transplants showed improvement in motor abnormalities. These results raised the exciting possibility that the transplanting of brain tissue might eventually be used to treat neurologic diseases in humans.

After extensive experimental work in rodents and limited experimental work in lower primates, Swedish surgeons began to implant autologous adrenal tissue stereotactically into the caudate nucleus or putamen of patients with advanced Parkinson's disease. None of the patients experienced more than transient benefit. Surgeons in Mexico City, however, have reported persistent improvement after transplanting adrenal medullary tissue to the caudate nucleus. The patient selection and the operative procedure used by the Mexican surgeons were different from those of the Swedish team. The patients treated by the Mexican group were much younger than those in the Swedish study, who were more typical of patients with Parkinson's disease. The Mexicans used an open craniotomy and placed the adrenal grafts at the head of the caudate nucleus in contact with the cerebrospinal fluid, which may contain trophic factors that promote transplant survival. Two of the patients operated on by the Mexican group died within 45 days of causes apparently unrelated to the operation.

Although highly experimental, the adrenal-to-brain transplant must now be considered of possible clinical significance. Similar transplantation programs have been started at centers in the United States, but the more recent reports from several of these centers suggest no benefit from such transplants, and the authors urge caution in expanding ongoing human research.

Parkinson's disease is not the only neurologic disease in human which brain tissue transplantation may eventually play a role. Neuroendocrine disorders, including genetic deficiencies of vasopressin and gonadotropin-releasing hormone in rats, have been ameliorated by fetal transplants. Fetal septal grafts can functionally reinnervate the hippocampus and dentate gyrus of adult rats after septal-hippocampal lesioning. The potential application to Alzheimer's disease has intrigued many researchers. Experimental work with animal models of traumatic and ischemic brain injury is also in progress. The development of brain tissue transplantation as an experimental therapy for a variety of neurologic diseases must await further basic research in rodents and lower primates.

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Lumbar Stenosis in the Elderly

PERSONS 60 YEARS OF AGE or older are susceptible to lumbar stenosis caused by degenerative disease, hypertrophied articular facets, thickened ligaments, and herniated discs. This elderly population tends to have associated medical problems that potentially increase their surgical risks, but with the ever-increasing number of elderly people, more will be referred to neurologic surgeons for help.

Characterized by low-back pain with distal radiation, lumbar stenosis causes poorly localized pain that mimics intermittent claudication of an ischemic origin. Pain may be well lateralized in the lateral recess syndrome. Walking or standing usually increases the pain; flexion of the lumbar region, however, may alleviate it. The common differential diagnosis is vascular claudication, which causes severe calf cramping that can be relieved by standing and decreased exercise.

Several recent studies have shown that elderly patients who are medically stable do well after surgical decompression by laminectomy. Surgical intervention is indicated when pain hinders a patient's mobility. Absolute indications for an operation are weakness and bowel or bladder dysfunction. Conservative therapy, including bed rest and flexion exercises, can be tried if pain is not intolerable and no other

neurologic deficits exist. The surgical procedure is laminectomy with foraminotomy and undercutting of the facets, if needed. Although uncommon, articular microdiscectomy is done when a herniated disc is seen.

In a recently reported series, 74 elderly patients underwent lumbar decompressive procedures. Most of these patients had acquired stenosis with a minor component of trauma. All had back (70%), leg (83%), or thigh (35%) pain. About a third had gait dysfunction, and less than 10% had incontinence. The mean duration of pain was more than six years. About 25% of the patients had associated medical illnesses such as hypertension and angina. The radiologic evaluation was primarily a myelogram with a computed tomographic (CT) scan; magnetic resonance imaging, however, being noninvasive and providing excellent anatomic resolution, is gaining popularity with neurologic surgeons and replacing the myelogram-CT scan combination. The surgical outcome was similar to that in other recent reports—more than 80% had significant improvement with either no pain or the occasional use of analgesics. Less than 5% were left unchanged after the operation, and no one was made worse.

Patients are able to tolerate symptoms of lumbar stenosis longer (average, six years) than they are cervical stenosis (average, two years). A loss of hand function is more debilitating than a loss of lower extremity function, causing patients to seek medical treatment sooner for cervical stenosis.

Surgical treatment must involve full decompression of the cauda equina and roots for successful recovery. If needed, the medial aspects of the facet should be removed to ensure that the existing root is adequately freed. The rarely encountered free fragment of disc is removed, but, to help provide stability, bulging disc with an intact annulus and posterior facets is not removed. Vertebral subluxation is rare after the operation because only the medial aspect of the facets is removed and the joint is kept intact. Mild symptoms caused by vigorous exercise or radiologic findings without symptoms should not be criteria for an operation. These patients should be observed clinically, and only when symptoms and signs are severe should repeat radiologic studies be done.

Age is not a contraindication for lumbar decompression for a medically stable patient. Patients have typical signs and symptoms that in the future can be evaluated by MR imaging. Surgical treatment must achieve full decompression to be successful with maintenance of the facet joints for stability. Asymptomatic patients with radiologic findings are not surgical candidates.

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Central Nervous System Diseases in AIDS

THE NUMBER OF PATIENTS with the acquired immunodeficiency syndrome (AIDS) has continued to double every year. By April 1988, there were more than 60,000 cases of AIDS reported to the Centers for Disease Control (CDC) in Atlanta. Epidemiologic studies have shown that 39% of such patients manifest significant neurologic disease at some time during their life and that the neurologic symptoms were the first manifestations of AIDS in 10%. Furthermore, intracerebral mass lesions will develop in 10% of all AIDS cases, so we can assume there have already been 23,400 cases of neurologic disease and 6,000 of intracranial masses associated with the present epidemic.

Computed tomographic (CT) brain scans carried out in patients with neurologic symptoms show focal lesions in 38% and atrophy in 33%; they are normal in 29% of cases. The causes of focal lesions include *Toxoplasma* abscesses (50% to 70%), primary central nervous system (CNS) lymphomas (10% to 25%), progressive multifocal leukoencephalopathy (10% to 22%), *Candida albicans* abscesses (3%), cryptococcomas (2%), Kaposi's sarcoma (2%), tuberculous abscesses (1%), and focal viral encephalitis (1%); no specific etiology can be documented in 10% of cases. All causes but progressive multifocal leukoencephalopathy can produce intracerebral masses.

The treatment of intracerebral mass lesions is usually a presumptive three-week trial of the anti-*Toxoplasma* agents pyrimethamine and sulfadiazine. If the masses shrink on that therapy alone, it is presumed that the patient harbored a *Toxoplasma* brain abscess, and that regimen is continued for life. If corticosteroid therapy had been instituted, it must be discontinued, and the lesion must not recur before the presumptive diagnosis of toxoplasmosis is made. If any or all of the masses enlarge at any time during therapy, or if they do not shrink by three weeks, it is unlikely that *Toxoplasma gondii* is the cause. A CT-directed stereotactic biopsy is recommended for any remaining lesion. The low risk—1% mortality or major morbidity—of CT stereotaxy, done with the patient receiving local anesthesia, and the likelihood of finding a treatable cause of the mass (>85%) combine to make such a surgical approach a viable option in these highly selected cases.

Primary CNS lymphomas in patients with AIDS are the same high-grade B-cell malignant tumors and produce similar symptoms as the primary CNS lymphomas that develop in the absence of immunosuppression. These lesions respond to radiation therapy—4,000 rads over three weeks—in more than 85% of cases when evaluated by CT scan and neurologic examinations. Patients' survival is increased threefold to fourfold over that of nonirradiated cases. Unfortunately, the systemic illnesses associated with AIDS are wholly responsible for limiting patients' survival to a few months; improved treatment of the systemic illnesses is bound to increase the clinical impact of successful lymphoma therapy. Because in 1.9% of all patients with AIDS, a primary CNS lymphoma will develop, and CDC predictions for 1991 include 74,000 new cases with a total of 145,000 receiving treatment during that year, the influence of AIDS on neurooncology can be estimated. It is possible that 1,848 primary CNS lymphomas will be diagnosed in 1991; this number approximates the 1,500 low-grade gliomas and 2,250 meningiomas treated yearly in the US.

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Controversies in Carotid Endarterectomy

THE PRACTICE OF CAROTID ENDARTERECTOMY has in recent years been the focus of tremendous controversy, which has revolved around three issues: efficacy with regard to preventing stroke, the appropriateness of patient selection for the procedure, and the surgical complication rate.

The only randomized controlled studies comparing the efficacy of carotid endarterectomy with that of medical management for preventing stroke and death have yielded equivocal results. Some clinicians have attributed this to the high perioperative complication rates found in these studies, which were done more than 15 years ago. They point out that the stroke incidence was significantly reduced in patients with a successful—that is, an uncomplicated—operation. A number of other reports of nonrandomized clinical trials suggest that carotid endarterectomy can reduce stroke risk, but definite proof of its efficacy must await the completion of several ongoing clinical trials.

More than 100,000 carotid endarterectomies were carried out in the United States in 1985, and about half of these were done in patients without transient ischemic attacks (TIAs) of a carotid artery distribution. A recent multicenter review of the indications for carotid endarterectomy found that almost a third of the procedures were considered inappropriate according to criteria derived from the medical literature by a panel of experts. The indications for carotid endarterectomy can, in general, be rated as follows:

Appropriate
- Hemispheric TIAs or amaurosis fugax associated with ipsilateral severe carotid stenosis (greater than 70% diameter reduction) or with a large, complex, ulcerated carotid plaque

Equivocal
- Completed stroke associated with severe stenosis or ulceration
- TIAs or amaurosis fugax with moderate stenosis (50% to 69%)
- Asymptomatic patients with severe stenosis

Inappropriate
- Any symptom category associated with a nonulcerated, minimally stenotic lesion (less than 50%)
- Patients with high surgical risk, such as the American Society of Anesthesiologists class 5.

Perioperative complication rates reported for carotid endarterectomy may vary from 1.5% to more than 20%, with most multicenter studies showing rates between 5% and 10%. A rate of postoperative mortality and disabling neurologic deficit much above 5% appears to negate most of the potential benefit of carotid endarterectomy. Reported clinical experience suggests that electroencephalographic monitoring, selective shunt use, meticulous surgical technique, intraoperative completion angiography, and cerebral protection with the use of barbiturates can reduce the rate of complications.

Controlled randomized studies of carotid endarterectomy currently underway should answer the most important questions regarding efficacy and safety. Until the results of these studies are available, carotid endarterectomy should be reserved for the treatment of patients with carefully established indications, and its performance should be limited to surgeons and at hospitals with acceptable complication rates.

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Natural History of Cerebral Aneurysms

TO DETERMINE THE EFFECTIVENESS OF THERAPY for cerebral aneurysms, the natural history needs to be defined. This is especially the case today because advances in medical technology have allowed surgical and radiologic access to complex vascular lesions in the brain. Such information concerning the natural history allows physicians to make rational decisions concerning treatment modalities.

Patients who have a cerebral aneurysm usually present after the aneurysm has ruptured, causing a subarachnoid hemorrhage (SAH). The average age at which an aneurysmal SAH occurs is 48 years. Frequently patients will experience a minor "warning" hemorrhage that will present as a severe headache days to weeks before a subsequent major cerebral hemorrhage.

Some studies suggest that 10% to 15% of patients with aneurysmal SAH die immediately after hemorrhage and before admission to hospital. If consigned to nonsurgical therapy, the remaining patients have on average a 50% mortality by the end of six months. There are three common causes of death: the original hemorrhage with an intracerebral hematoma; the subsequent occurrence of cerebral vasospasm; and rehemorrhage. The microsurgical clipping of ruptured aneurysms is specifically designed to prevent the highly lethal rehemorrhage. The risk of rehemorrhage—in some studies as high as 50%—is particularly great during the first few days after the initial hemorrhage. Mortality at six months in conservatively treated patients is strongly correlated with the neurologic grade on admission: grade 1 (normal), 15%; grade 2 (stiff neck and headache), 30%; grade 3 (lateralizing neurologic signs), 50%; grade 4 (decreased level of consciousness), 65%; and grade 5 (comatose), 90% to 100%.

If conservatively treated patients survive their initial bleeding episode, they do not remain free of the risk of a subsequent rehemorrhage. Long-term studies indicate that patients whose aneurysms have ruptured and who survive the initial acute period—the first six months—face a 3% to 5% risk per year of subsequent rehemorrhage with an associated 60% mortality.

Whereas the natural history of ruptured aneurysms is relatively well defined, the natural history of unruptured aneurysms is less well understood. Because of the high mortality (and morbidity) associated with the rupture of a cerebral aneurysm, attention has been focused recently on attempting to define the hemorrhage rate of intact cerebral aneurysms. Most studies suggest a risk of 1% to 2% per year for patients whose cerebral aneurysms are discovered accidentally during cerebral angiography, computed tomographic or magnetic resonance scanning, or evaluation for multiple subarachnoid aneurysms. A size greater than 10 mm and systemic hypertension may increase the risk of hemorrhage.

Given the preceding considerations and the relatively low risk of operations on unruptured aneurysms, in recent years

the preferred management of asymptomatic, unruptured aneurysms has been surgical, assuming the patient is healthy and the aneurysm is accessible.

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Editorials

Physician-Subsidized Health Care

ELSEWHERE IN THIS ISSUE an admittedly less than perfect study provides some insight into the extent to which physicians, at least in San Francisco, think they are subsidizing health care in their community. Even if the figures are substantially overstated and by a self-selected segment of the physician population in San Francisco, they are impressive. They also suggest how far we have drifted from the loudly proclaimed social goal of the 1960s, which was to eliminate "demeaning" charity from patient care. Charity in health care has continued to be with us. No one thinks that it was ever completely eliminated.

In any case, these are the 1980s, soon to be the 1990s, and the resources for needed charity are coming under severe strain. The social programs that were expected to eliminate "demeaning" charity and assure dignity in health care regardless of the ability to pay have simply failed to do this. More and more of the third-party payers in both the public and private sectors are either unwilling or unable to pay the true costs of patient care. Paradoxically, the human and technologic resources for health care exist in relative abundance—certainly this is true in San Francisco—but there are not sufficient dollars to pay for care that is presently uncompensated yet needed. The burden of taking care of those who cannot pay the real costs is being carried by the charity that community hospitals, practicing physicians, and others in the health care field are willing and fiscally able to provide. It seems more and more evident that the fiscal capacity for this charity is limited and may soon be exceeded by the need for it.

There are recognizable, inescapable basic costs to rendering uncompensated care, and if these costs cannot somehow be met, there will be no uncompensated care, no matter how good the intentions are of those who would want to provide it. The fiscal squeeze has been on hospitals, physicians, and local communities for some time now, and in certain programs for the needy the costs of rendering care have already begun to exceed the revenues available to pay those costs. The fat is now pretty well out of the system, and there are signs that the bone and the muscle are beginning to be cut away.

As one ponders this prospect of inadequate or unavailable health care for those who may need it most, one wonders if a way might be found to make whatever dollars are available for indigent care more readily available to be used more efficiently where the care is needed—that is, in the local communities or perhaps in some kind of community-based health care regions, possibly under the jurisdiction of a community or regional authority that would be relatively free of inefficient and costly interference and restriction from state and federal governments. As it is, the sources of the dollars are all far from the real human action in health care. Federal and state programs have now been shown not to meet the need. Perhaps their administration and control have been just too remote to be able to function efficiently and effectively at a local level, where health care dollars could be applied in response to human needs and within a framework of human relationships. Maybe it is time to streamline the system and give decentralized local communities and health care regions more of the financial resources and more responsibility for how they are spent, and thus allow them a better chance of solving their own problems in what might prove to be more sensitive ways.

MSMW

Medicare Payment Reform—A Practitioner's Perspective

AS THE PHYSICIAN PAYMENT REVIEW COMMISSION attempts to find ways to restructure Medicare financing for physicians' services, the perceptions of practicing physicians and the way in which they are paid for the work they do tend to vary with their specialty. All parties have many axes to grind. Consequently, Lee and Ginsburg have their work cut out for them if they are to truly build a consensus on the Medicare payment reform they discuss elsewhere in this issue.

Questions of physician payment tend to arouse powerful emotions within and outside of medicine. It is sobering to think that in the last months of 1987, underpaid physicians in Peru struck for higher wages and were teargassed after throwing rocks during a clash with the police. In several countries there are physicians who cannot find a job or who must move to remote areas in order to earn a living wage.

Physicians in the United States have been lucky, but, then again, so have many other Americans. The 1987 average remuneration (salary and fringe benefits) for industrial workers in this country reached $50,000 a year. The average physician now earns more than double that amount. But the average primary care physician does not.

Medicare has been a major contributor to physicians' incomes. In retrospect, the opposition of the American Medical Association to the creation of Medicare seems extraordinary. Few, if any, other "industries" would have rejected such largess, especially since the burden of charitable care had also been removed with the creation of Medicaid. The much-feared concurrent government regulation has also been much slower in coming than many would have predicted.

The climate in which medicine is practiced has changed. The 1965 blend of charitable and fee-for-service care has yielded to the 1988 fixation on the bottom line. There is more money but less honor in medicine. And there are nearly 40 million Americans without any health insurance. At the same time, the approach toward physicians has changed. We are increasingly being viewed as economic animals to be manipulated into compliance by each and every program of the moment: from healer to puppet in a little more than 20 years.

Medicare sends confusing signals. There is more pay for a home visit by a nurse than by a physician. Chiropractic adjustments constituted the ninth most common service paid by Medicare in 1983—procedures for which there is public demand but with little in the way of agreement regarding necessity, utility, or quality. Preventive medicine is not covered by Medicare, but the National Institutes of Health continue to promote it vigorously.

Fee-for-service practice is now burdened with administrative requirements that force an increasing amount of both physician and staff time to be directed away from patient care. Examples are the explanation of maximum allowable actual

charges and compulsory lab assignment and the latest requirement that a clinician anticipate what Medicare may not pay for (or how much it will pay if it does pay) and refund any money collected unless a signed agreement to pay has been obtained in advance—in a form that has yet to be described.

These are admittedly small items in the grand scheme of health care financing, but they threaten to wreck the everyday practice of medicine. There is reason to think that the government has become less interested in enticing more physicians into becoming participating physicians and accepting assignment for all Medicare patients. Instead, there is now a heavy-handed effort to coerce physicians into doing so by making life unbearable for those who do not.

The frustration of costly and time-consuming administration and of coping with downgraded and disallowed services undoubtedly is a contributor to the higher volume of billed services per recipient that has recently been noted. It also threatens to produce a numbing conformity as it rapidly becomes apparent that anything falling outside the computer screens will lead to an involved explanation and perhaps an accusation of performing "unnecessary" services. Thus, it may be more prudent to admit to hospital a patient needing a second electrocardiogram within a 30-day period than to obtain one in the office. Similarly, it makes some kind of sense to send a patient with pulmonary edema to an emergency department to receive intravenous furosemide rather than administer it in the office. The latter technique has been turned down for payment on the grounds that it is not covered on the same day as an office visit. These are actual events. There seems to be no recognition that extra services may be needed to avoid even more costly care, or, if there is recognition, the question is ignored because it is so hard to evaluate the circumstances quickly.

The Physician Payment Review Commission considers that fee-for-service medicine will continue to play an important role in the future. Indeed, the commission has resisted some administration proposals that would sharply decrease the role of fee-for-service: for example, Medicare preferred provider organizations and the conversion of corporate retired employee benefit plans into capitated programs known as MIGs (Medicare insured groups). The commission's attitude toward the "cognitive-procedural" question is not entirely known at this time. For the moment, Congress, in the 1987 budget act, called for preferential treatment for office, home, and nursing home visits. Lee has endorsed this position by suggesting the annual Medicare update be allowed for these services but deferred for all other services at the present time.

On the other hand, Ginsburg pointed out in an interview (*The Internist,* May-June 1987, p 23) that should there be substantially inequitable underpayments for some widely used services, such as office visits, satisfactorily redressing such an inequity would require large decreases in the reimbursement for other services to generate the necessary funds. This assessment would seem to validate the long-held view of some "procedural" specialists that any increase in "nonprocedural" fees would only come entirely at their expense. Concerned about just such a possibility, the American College of Radiology cut its own fee deal with Congress last year. The entire issue is potentially highly divisive, and one prominent commentator has suggested that quarrels over physicians' incomes may lead to an important decline in the current political power of physicians (*The Wall Street Journal,* February 9, 1988, p 30).

Another source of difficulty with consensus—if the term is intended to include the medical profession—comes from the repeated statement that proposed changes must be both budget-neutral and also protect beneficiaries against increased out-of-pocket expense. This, of course, is the congressional mandate to the Physician Payment Review Commission. But in the face of an aging population and increasing technology—much of it cost-raising rather than cost-lowering—and of the undiminished social expectations of medicine, this may prove impossible. By implication, physicians may expect a series of progressive fee cuts when even extraneous factors cause budgetary shortfalls. The reduction of some surgical fees on the basis of "inherent reasonableness" may be the first such exercise. The reason for thinking so is that there is to be a coincident reduction in laboratory reimbursement of approximately 8%, already subject to mandatory assignment, that will have a further negative effect on the economic position of the primary care specialties. Thus, lean cats as well as fat cats are being targeted, and all cats are affected by across-the-board governmental payment cuts such as the Gramm-Rudman-Hollings reductions.

In such a climate, any pressure for mandatory assignment is particularly worrisome. Experience with Medicaid (validated by surveys by the California Medical Association) has shown that physicians are less concerned by lower pay than by arbitrary and unpredictable behavior by fiscal intermediaries. The latter upsets and frustrates office staff and affects overall performance in the care of all patients.

Mandatory assignment also creates a conflict of interest between physicians and patients. Under nonassigned billing, a patient suffers extra out-of-pocket expense when Medicare reimbursement is deficient. In the case of assigned claims, the patient has no balance due should Medicare fail to pay the physician for a legitimate service. Should Medicare underpay the physician, the 20% balance due from the patient will be less than if the proper fee were recognized. Thus, under mandatory assignment, the patient is either insulated from the question of how physicians are paid or has a bias toward lower levels of compensation.

This discussion has so far not acknowledged that there is a problem with both overcharging and billing for unnecessary services. These are the Achilles' heel of fee-for-service medicine, and they must be stopped. At the same time, the fee-for-service segment of health care is the one with the greatest incentive to please patients and to innovate. Despite its shortcomings, it serves a vital role as a counterpoise to managed care and capitated plans, which would have less incentive to provide a maximum level of care were it not for competition from the fee-for-service segment. Thus, I think fee-for-service medicine needs both supervision *and* protection. Administering it into oblivion will be counterproductive.

Certain factors indirectly bear strongly on physician reimbursement. I am especially concerned that 70% of Medicare payments go to 9% of the insured, that care in the last year of life consumes up to half of all Medicare funds, and that terminal illnesses consume a third. At the same time, preventive medicine is excluded. These figures suggest a gross distortion of policy that must, of necessity, distort physician reimbursement.

Better funding of Medicare would allow more flexibility in designing ways to pay physicians. It seems incongruous

that many patients older than 65 are well-to-do, yet are "protected" against physicians by mandatory fee freezes and service restrictions. In the aggregate, the 65-plus decade is the second wealthiest in the nation. Nevertheless, this group does not share in paying for inflationary increases in a physician's cost of doing business, leaving these increases to be passed on to younger people, who are often less affluent. It is not even clear that it is legal to treat people of Medicare age *outside* the Medicare program. The current attempt to lump the care of all senior citizens, regardless of personal resources or attitude toward health care, into a uniform mold promises to backfire badly should this continue as a key element in health policy.

Some form of tiered care may be the only satisfactory answer. In Britain and Canada, with their much-acclaimed but monolithic systems, there are increasing complaints of poor and delayed service, underfunding, and misallocation of resources. It simply seems foolish to head directly along the same course in the United States.

Primary care may require entirely new approaches if it is to remain viable and keep its practitioners from lobbying for direct employment by the federal government. One such method might be to partially capitate care to provide a financial base and then pay relatively modest supplements for actual services rendered. Patient co-payments would be needed to balance the incentives.

If the entire Medicare program is to remain solvent, it also would seem wise to attempt to recoup some of the money spent on terminal care. This might even be used as a start toward paying for more long-term care, a subject of great current interest to the American Association of Retired Persons. In the case of the affluent elderly who leave no surviving dependents, there seems little reason not to have the government, through a lien on the estate, attempt to recoup at least a part of the funds spent on terminal care. Safeguarding estates at the expense of the public hardly seems like sound social policy.

There must be innumerable ideas for improving Medicare. Not all will be the product of consensus panels. Though this technique has a sound social and political basis, its use in policy-making in clinical areas should remind us that it will not automatically bring forth the most effective or innovative approaches.

Lee and Ginsburg put it well when they say, "One central challenge . . . is to find a way to incorporate society's concerns about limited resources into physicians' decision making while maintaining the physician's freedom and responsibility to exercise clinical judgment on behalf of the patient."

Amen.

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Further Comments on Chronic Arsenic Poisoning

ARSENIC POISONING is still with us, as Dr Gorby has reported elsewhere in this issue, and we need to be vigilant to diagnose it. The features of arsine poisoning and acute poisoning from inorganic arsenic compounds are well defined and easy to recognize, but the features of chronic poisoning from small amounts of inorganic arsenic repeatedly administered are insidious and nonspecific; the patient feels tired and listless and experiences generalized muscle weakness, paresthesia and numbness in the extremities, and anorexia and general malaise. Chronic arsenic poisoning in humans is usually derived from iatrogenic sources, from working in the smelter industry, or from exposure to inorganic arsenic compounds in water supplies (usually domestic water wells).

Fowler's solution (1% potassium arsenite) was used for many years as a tonic and for the treatment of psoriasis and asthma. The prolonged use of this medication produces chronic arsenic poisoning and, although it was withdrawn from use in the 1950s, cases of poisoning still occasionally occur; we reported in 1979 the case history of a patient who presented with hematemesis from esophageal varices that were the consequence of presinusoidal portal hypertension, a known complication of chronic arsenic poisoning.[1] He had been taking an arsenic-containing tonic daily for 55 years and had the obvious dermatologic features of chronic arsenic poisoning; his hair arsenic level was 11.7 parts per million (ppm; normal less than 1). It should be remembered that skin cancer is common in patients with arsenic-induced hyperkeratoses. Arsenic-containing medications are still widely used in herbal remedies in the Far East.

Exposure to inorganic arsenicals, particularly arsenic trioxide and sulfides, may occur in workers employed in the smelting of nonferrous ores, particularly copper and gold, and several studies have reported an increased prevalence of lung cancer (particularly adenocarcinoma) in this industry.[2] Evidence of arsenic toxicity in smelter workers is usually confined to this increased prevalence of lung cancer, but neuropathy has also been reported in this group.[3] Although arsenic has been blamed for many other types of cancer, the only convincing association other than with cancer of the lung is with hepatic angiosarcoma, which may develop many decades after exposure has ceased.[4] There is also some evidence that arsenic may be mutagenic and teratogenic.[2] The study of arsenic carcinogenesis has been confounded by the lack of a susceptible animal model; Pershagen, however, has been able to produce lung cancer in hamsters by the intratracheal injection of arsenic trioxide mixed with charcoal carbon.[5]

Chronic arsenic poisoning may also occur from the continuous ingestion of small amounts of arsenic in domestic well water. Arsenic is widely distributed in natural rock formations, particularly the meguma group of gold-bearing rocks that are found in the northeastern, northwestern, and southwestern parts of the United States and in eastern Canada extending from the Atlantic Coast to the Manitoba border. Normally the arsenic is complexed as the relatively insoluble sulfides, but if the rock is worked and weathered, these compounds can be oxidized to the more soluble oxides and can enter the water supply. Surface water and shallow wells—less than 9 m (30 ft) deep—frequently are self-cleansing. Surface water, particularly when acid, frequently has a high iron content, and this matrix, particularly if it is well oxygenated, promotes the formation of insoluble iron-arsenic complexes that precipitate into the sediments; the lake sediments in eastern Canada can be rich in arsenic, but these appear to be stable. Conversely, deep wells may be heavily contaminated with soluble arsenic compounds as they often are more alkaline, and this reduces the solubility of iron. Also, these waters frequently exist under reducing conditions, and the reduced forms of arsenic and iron (arsenite and ferrous iron) do not co-precipitate to the same extent

as do their oxidized counterparts. Arsenic can, therefore, reach toxic concentrations in these wells and can produce serious chronic poisoning. We investigated two cases of severe chronic poisoning in Nova Scotia in 1977.[6] The patients were using a domestic well that had an arsenic content of 1.4 ppm (upper limit of acceptability, 0.05 ppm). Although theirs was a shallow well, it had been recently "limed"; it contained about equal amounts of the trioxide and pentoxide of arsenic.

The organ systems affected in chronic arsenic poisoning are the skin, the nervous system, and the vascular system. The pigmentation of chronic arsenic poisoning often resembles a simple suntan, especially in older people when the appearance of the latter is often mottled. The distribution of arsenic pigmentation is characteristic, however: it is particularly pronounced around the eyelids, nipples, axillae, groins, temples, and neck. Also, hyperkeratosis develops on the palms of the hands and the soles of the feet, and this is often surmounted by cornlike epidermal pegs that are easy to recognize. The vascular response to arsenic is reported to be an endarteritis that may produce gangrene of the extremities[7] and perhaps an increased prevalence of myocardial infarction, although this latter association has not been firmly established. The effects on the nervous system consist of a neuropathy that is often largely confined to the arms and the legs and is more pronounced distally. Sensory impairment is usually more pronounced than motor effects, and the legs may be more severely affected than the arms.[8] The patients complain bitterly of tingling and burning sensations in the extremities.

The assessment of the severity of chronic arsenic poisoning is usually made on clinical grounds, and this should include a careful, well-documented neurologic examination. Electromyography may help in individual cases, but the value of electromyography in assessing groups of patients exposed to minor degrees of arsenic contamination has not been fully established. Blood levels of arsenic are of little use in human arsenic intoxication, except perhaps to identify arsenic as the cause of acute poisoning in patients who are anuric; its rapid clearance from the blood—little remains after ten hours[9]—makes it an unsuitable analyte in other circumstances. Arsenic is rapidly and efficiently excreted in the urine, largely as methylated derivatives, and urine arsenic quantitation is therefore a reliable index of a recent exposure—one to two days previously. Normal urinary levels in the absence of arsenic exposure are less than 50 μg per liter, but it should be remembered that this can increase to 1.68 mg per liter after a seafood meal.[10]

Provided external contamination can be excluded, hair arsenic concentrations are a good indicator of chronic arsenic exposure and are approximately related to the severity of poisoning.[6] Because the arsenic is found on the outer surface of the hair both when the arsenic is externally applied and also when it enters the hair from ingesting by mouth, and because hair can concentrate arsenic manyfold,[11] external contamination when present negates the use of hair arsenic levels in assessing a case of chronic arsenic poisoning. Thus, arsenic should be sought in the soil around unsealed coffins and in the material surrounding an exhumed corpse in forensic cases in case contamination of the corpse from the soil has occurred. The likelihood of external contamination also limits the value of hair arsenic levels as a measure for assessing toxicity in the smelter industry; in patients employed in smeltering, urine arsenic concentrations would be a better index of exposure. Nail arsenic levels are also increased in chronic arsenic poisoning, but there is less information available on their interpretation than there is for hair. Nails are also subject to external contamination and also can concentrate arsenic.

Dr Gorby has comprehensively reviewed the chemistry and toxicology of arsenic and has outlined the various clinical features of arsenic poisoning that should be valuable reminders to observant physicians.

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Case Reports

Severe Hypokalemia Associated With Pseudohypoxemia in Acute Nonlymphocytic Leukemia

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LOW SERUM POTASSIUM CONCENTRATIONS are usually considered a consequence of internal shifts of potassium from the extracellular to the intracellular environment or of external losses of potassium (true potassium deficiency). Hypokalemia occurs in an estimated 40% to 60% of patients with leukemia[2,3]; conversely, leukemia is one of the more common diseases associated with severe hypokalemia.[4] It has been assumed that low potassium concentrations measured in the serum of these patients reflect true potassium depletion due to a peculiar renal wasting of potassium or, alternatively, to potassium being sequestered by an expanding tumor mass.[2,5,6] More recently it has been suggested that this electrolyte disorder can be an in vitro phenomenon.[7,8] In the following report, we describe a case of a patient with severe hypokalemia (serum potassium concentrations of 0.5 to 1.7 mEq per liter) and acute nonlymphocytic leukemia whose clinical presentation was not consistent with such severe potassium deficiency.

Report of a Case

A previously healthy 35-year-old woman seeking medical help because of malaise and fever for three weeks was found to have generalized lymphadenopathy and a whole blood leukocyte count of 518,000 per μl. On admission to the hospital, she appeared normal in size and development but in moderate respiratory distress. Her temperature was 39.5°C (103°F), blood pressure 128/74 mm of mercury, pulse 130 per minute, and respirations 30 per minute. She had a diffuse petechial rash, several bruises on the lower extremities, fine inspiratory rales at the bases of both lung fields, generalized lymphadenopathy, and an enlarged spleen. She was neurologically intact except for mild generalized weakness. Circulating leukocytes were identified as greater than 90% myeloid blast forms, consistent with acute nonlymphocytic leukemia. Her hemoglobin was 8.6 grams per dl, and the platelet count was estimated to be 15,000 per μl. A serum phosphorus level was 0.6 mg per dl, albumin 3.3 grams per dl, uric acid 2.9 mg per dl, glucose 146 mg per dl, blood urea nitrogen 4 mg per dl, and calcium 7.9 mg per dl. The electrocardiogram lacked any evidence of hypokalemia. A chest roentgenogram showed a diffuse interstitial infiltrate consistent with pulmonary leukostasis. The course of electrolyte change following hospital admission is shown in Table 1.

Chemotherapy with vincristine sulfate, cytarabine, and daunorubicin hydrochloride was started an hour after admission; broad-spectrum antimicrobials were added for what later proved to be *Staphylococcus aureus* sepsis. Leukapheresis reduced the leukocyte count to 342,000 per μl by the fifth hour. Despite infusing 170 mEq of potassium chloride over the first 12 hours, there was no improvement in the measured serum potassium concentration, as shown in Table 1. A urine potassium concentration after the infusion was 81 mEq per liter, and repeated electrocardiograms showed no signs of hypokalemia. Numerous complications arose, including sepsis, bleeding, and renal failure; despite intensive treatment including hemodialysis, she died on the third day of intracranial hemorrhage.

Comment

This patient's clinical state was inconsistent with a serum potassium level of 0.5 mEq per liter. She lacked cardiac manifestations of hypokalemia, and although there was weakness, the severity was less than expected for such a low serum potassium concentration. Furthermore, an intravenous infusion of potassium chloride in large amounts failed to raise the measured serum potassium level at the same time that urine potassium excretion approximated the infusion rate. The patient's arterial blood gas values also appeared to be inconsistent with the clinical data. Despite measured arterial oxygen tensions of less than 40 torr, she did not appear cyanotic, no respiratory compensation was observed, and the hemoglobin oxygen saturation was 97% to 100% by ear oximetry. Because spurious hypoxemia is known to occur in patients with leukemia,[9] we reduced the in vitro delay between arterial sampling and blood gas measurement, with resulting oxygen tensions of greater than 90 torr.

In an analogous manner, we decreased the in vitro delay before electrolyte measurements and found much higher serum potassium levels. When the in vitro time before centrifugation and separation of the serum was less than three minutes, potassium concentrations of 2.8 and 3.0 mEq per liter were obtained by flame photometry and ion-specific electrode, respectively (Table 1). A subsequent electrolyte measurement, delayed 20 to 30 minutes after the blood specimen was drawn, gave another low value of 1.6 mEq per liter. Inadvertent plasma dilution was not a factor, as evidenced by normal sodium, chloride, and total carbon dioxide levels in the same blood specimens. These findings confirmed clinical impressions that routine reports of potassium concentration by the clinical laboratory were spuriously low and that the patient's "hypokalemia" was actually a function of in vitro incubation times.

Hypokalemia associated with leukemia has been reported in more than 40 papers describing more than 130 cases since 1966. True potassium deficiency has been documented in some instances, but most cases have puzzled physicians seeking causes for the disorder.[2,5,6] High urine potassium concentrations, recorded in most of these patients, have suggested primary renal wasting; yet, no mechanism or cause of enhanced renal potassium secretion has been uncovered. Ex-

(Depner TA, Magee JA: Severe hypokalemia associated with pseudohypoxemia in acute nonlymphocytic leukemia. West J Med 1988 Sep; 149:332-334)

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cretion of lysozyme, a suspected tubular toxin, has correlated poorly with the occurrence of hypokalemia.[2,3] There is a conspicuous lack of symptomatic hypokalemia, electrocardiographic abnormalities, or aldosterone-renin changes of hypokalemia despite serum potassium levels of less than 2 mEq per liter.[2,3,5,6] In reviewing these reports, we found no mention of clinical responses to administered potassium supplements. These observations suggest that many of the reported leukemic patients actually had normal serum potassium concentrations (Table 2).

Failure to recognize spurious hypokalemia in patients with leukemia by others in the past could be related to a conceptual conflict with pseudohyperkalemia, well known to occur in patients with leukocytosis or thrombocytosis and also found to be dependent on the in vitro incubation time.[10] In patients with certain types of leukemia, the measured potassium concentration may be a complex function of the time in vitro, possibly the net effect of a stimulated uptake of potassium by these malignant cells or erythrocytes balanced by leakage of potassium across membranes that have been shown to have altered permeability to cations.[11,12]

Potential stimuli for the leukocyte uptake of potassium in vitro that does not occur in vivo include depletion of oxygen or metabolic substrates, clotting, a decrease in temperature, exposure to glass or other surfaces, or the release of tissue factors. A mechanism for pseudohypokalemia was proposed by Naparstek and Gutman, who noted previous work on cation permeabilities and sodium-potassium adenosine triphosphatase (Na^+-K^+ ATPase) in normal and leukemic leukocytes.[7] Leukemic cells, especially immature blast forms, have been found to have higher Na^+-K^+ ATPase activity, higher sodium permeability, and higher respiratory activity than normal cells.[11,12] A primary defect in sodium permeability would lead to higher intracellular sodium concentrations, stimulating ATPase and cellular potassium uptake. The finding of spurious hypoxemia in association with pseudohypokalemia in our patient may be due to the increase in respiratory activity required to support this energy-consuming transport process. Further studies of hypokalemia in cases of leukemia will shed more light on the possibility of a serum factor that causes altered cell membrane transport or permeability to potassium.[7]

The practice of infusing large amounts of potassium intravenously in patients with leukemia-associated hypokalemia must be questioned. Such infusions, especially in oliguric patients with a normal potassium balance, may have serious consequences in a setting where high morbidity and mortality are easily attributed to the underlying leukemia or to chemotherapy. Rapidly determining serum potassium concentrations may help to distinguish this form of pseudohypokalemia from true potassium deficiency and avoid the risks of infusing potassium in patients who have leukemia.

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TABLE 1.—*Laboratory Studies in a Patient With Acute Nonlymphocytic Leukemia Over the First 48 Hours of Hospital Admission*

Time After Admission, hr	Leukocyte Count, $\times 10^3/\mu l$	Blood Chemistry Levels: Sodium, mEq/liter	Potassium, mEq/liter	Bicarbonate, mEq/liter	Creatinine, mg/dl	Arterial Blood Gases: Fio_2, %	Po_2, torr	Pco_2, torr
0	518	136	1.5	26	1.0	21	33	44
3	...	134	1.4	24	0.9	100	54	43
5	342	137	1.1	25	0.9	...	...	..
8	...	...	1.7	..	...	...	...	..
12	334	142	0.5	29	0.9	100	67	41
13	...	...	0.6	..	...	...	...	..
16	...	...	1.7	..	...	...	...	..
18	332	144	0.5	28	1.0	80	53	39
19	278	...	2.8*	..	...	...	...	..
			3.0†					
23	278	...	2.6	..	...	...	...	..
29	278	144	1.6	26	1.3	50	56	39
36	...	...	3.4	..	...	...	...	..
48	27	139	4.8	22	2.8	50	103	38

Fio_2=fraction of inspired oxygen, Pco_2=carbon dioxide pressure, Po_2=oxygen pressure

*Flame photometry—in vitro time=3 minutes.
†Ion-specific electrode—in vitro time=3 minutes.

TABLE 2.—*Tests of Proposed Theories to Explain Hypokalemia in Leukemia*

Theory	Observations: No External Loss of K^+ Seen	High Urine $[K^+]$	Lack of Clinical Hypokalemia	Failure of IV K^+ Therapy	Lack of Renin-Aldosterone Response
Renal leak due to lysozymuria or other factors	+/−	+	−	+/−	−
Hyperkaluria due to drugs	+/−	+	−	−	−
In vivo uptake of K^+ by tumor	+	−	−	+/−	−
In vitro uptake of K^+	+	+	+	+	+

IV=intravenous, K^+=potassium ion, +=theory fully accounts for observation, +/−=theory partially accounts for observation, −=theory does not account for observation

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Echocardiographically Silent *Aspergillus* Mural Endocarditis

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As predicted by Zimmerman[1] in 1950, invasive mycotic infection has increased in frequency and importance. Aging of the population and burgeoning numbers of hosts compromised by severe underlying disease or immunosuppressive therapy are felt to account for this phenomenon.[2,3] Aspergillosis has increased in incidence at a disquieting rate and has now become the third most common of the systemic mycoses.[2]

Embolization to peripheral vessels is a hallmark of *Aspergillus* endocarditis.[4] Valvular vegetations are the usual source. We describe a case remarkable for a mural location of an echocardiographically silent *Aspergillus* vegetation and for the associated difficulty in establishing a diagnosis of endocarditis.

Report of a Case

The patient, a 42-year-old nurse with a 20-year history of systemic lupus erythematosus complicated by Raynaud's phenomenon with recurrent ulcerations, was admitted to Henry Ford Hospital (Detroit) because of digital gangrene. Medications included prednisone, 20 mg per day, and azathioprine, 150 mg per day. On admission, fever and cough developed with new bilateral upper lobe nodular infiltrates. A transbronchial biopsy specimen of a left upper lobe nodule showed nonspecific inflammatory findings, but no bacteria, mycobacteria, or fungi were cultured. The total serum hemolytic complement was diminished, and the erythrocyte sedimentation rate was elevated. The prednisone dose was increased to 60 mg per day, then tapered to 10 mg per day. The digital gangrene and pulmonary infiltrates, which were interpreted as manifestations of her systemic lupus erythematosus, resolved.

Six months later, she was readmitted with digital gangrene of the left hand. Her temperature was 37.6°C (99.7°F). The distal left upper extremity was tender, cold, and cyanotic. There were no splinter hemorrhages or funduscopic findings. On cardiac examination there were no murmurs, gallops, or rubs. Her chest was clear to auscultation; an x-ray film of the chest was normal. The leukocyte count was 6,400 per μl (95% polymorphonuclear leukocytes, 2%

Figure 1.—The photograph shows a surgically excised "thrombus" that extended into the left palmar arch.

Figure 2.—A histologic section of "thrombus" shows dichotomously branching, septate hyphae (Grocott-Gomori methenamine-silver stain, original magnification × 630).

(Lang DM, Leisen JCC, Elliott JP, et al: Echocardiographically silent *Aspergillus* mural endocarditis. West J Med 1988 Sep; 149:334-338)

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bands, 1% lymphocytes, and 2% monocytes), and the hemoglobin was 10.3 grams per dl. Electrolyte levels, a urinalysis, prothrombin time, partial thromboplastin time, a platelet count, and assays for C3, C4, and CH_{50} were normal.

Aspirin, dipyridamole, intra-arterial reserpine, and topical nitroglycerin were given, and a stellate ganglion block was done without improvement. A "thrombus" that extended into the palmar arch was removed from the left ulnar artery (Figure 1). Dichotomously branching, septate hyphae were seen on microscopic examination (Figure 2), and *Aspergillus fumigatus* was cultured from the thrombus but not from four (venous and arterial) blood specimens. The prednisone dose was tapered, and antifungal therapy with amphotericin B, 0.6 mg per kg body weight per day, was initiated. A chest x-ray film and an electrocardiogram were normal. An M-mode and two-dimensional echocardiogram (Hewlett-Packard, Ultrasound Imaging System, Andover, Mass; 2.5-MHz transducers) showed no vegetations, normal cardiac chambers, and a small pericardial effusion.

On the 13th hospital day, numbness and cyanosis of the right foot developed abruptly. A clot containing hyphal elements, which grew *A fumigatus,* was removed from the right anterior and posterior tibial arteries. Flucytosine (5-fluorocytosine), 150 mg per kg per day, and rifampin, 600 mg per day, were added to her regimen. Three additional echocardiograms—M-mode and two-dimensional—were done serially on the 14th, 17th, and 21st hospital days and were unchanged. There were no echoes to suggest a valvular or a mural lesion. A digital subtraction angiogram of the aorta and pulmonary circuit, computed tomography of the head and sinuses, renal and liver-spleen scans, and serial electrocardiograms were done from the 14th to the 22nd hospital days and did not reveal a significant abnormality.

On the 23rd hospital day, an exploratory cardiotomy was

Figure 3.—The photomicrograph shows necrotizing inflammation of a specimen of left ventricular endocardium and myocardium (periodic acid-Schiff stain, original magnification ×14).

Figure 4.—A higher magnification (×102) of the same lesion as in Figure 3 shows *Aspergillus* hyphae (periodic acid-Schiff stain).

done. Inspecting the surface of the heart revealed no abnormality. Exploring the proximal pulmonary veins by Fogarty catheter also showed no abnormalities. The findings of a visual inspection of the aortic and mitral valve leaflets were unremarkable. A 5-mm cylindrical excrescence was found on the anteromedial papillary muscle and its adjacent chordae tendineae. Microscopic examination of periodic acid-Schiff-stained endocardial and myocardial tissue showed necrotizing inflammation (Figure 3) containing dichotomously branching, septate hyphae (Figure 4). The mitral valve and papillary muscle were excised and replaced with a porcine xenograft. Cultures of specimens of mural endocardium, clear pericardial fluid, and mitral valve yielded *A fumigatus.*

The postoperative course was complicated by a fluid overload and pneumonia *(Enterobacter cloacae)* with ensuing respiratory failure. On the fifth day following the cardiotomy, refractory hypotension developed, and death ensued. An autopsy was not permitted.

Discussion

This report suggests that in an immunocompromised host presenting with peripheral mycotic embolization, a diagnosis of mural endocarditis should be suspected even when vegetations are absent on serial echocardiograms. Cardiotomy may be required to confirm the diagnosis. The optimal management of mural endocarditis has not been established; we would recommend, however, surgically excising the vegetation and circumjacent involved endocardium and myocardium to remove a possible source for further embolization and giving combination antifungal chemotherapy.

Embolization to major vessels was first heralded by Andriole and co-workers as characteristic of fungal valvular endocarditis.[5] This phenomenon has been confirmed particularly in *Aspergillus* species endocarditis.[4,6-8] In the first two reported cases of *Aspergillus* valvular endocarditis[1] and in 9 of 40 cases in a more recent review,[4] peripheral embolization was described. This latter review included six cases with mural involvement alone.[9-14] Of the remaining 34 patients in this series with valvular endocarditis, an antemortem diagnosis was achieved in 9 (26%). In eight of these cases, the diagnosis was established by a histologic examination and culture of specimens of excised emboli. *Aspergillus* emboli alone are not pathognomonic of valvular endocarditis, since a mycotic aneurysm of the thoracic aorta may present with embolization.[15] We would note from this and two other recent reports[16,17] that *Aspergillus* mural endocarditis may also have this presentation.

Infection of the endocardium may involve either its valvular or its mural components. The pathogenesis of valvular endocarditis relates to blood flow turbulence and resultant platelet or fibrin thrombi that become colonized with circulating microorganisms.[18] Mural endocarditis has been described in association with congenital defects,[19,20] prior infarction,[21] and damage from a transvenous cardiac pacemaker,[22] but may develop without a previous endocardial injury. Mural endocarditis may arise from a subendocardial focus or from the spread of adjacent infection.[19,23] Nonvegetative endocardial plaques may result from the extension of myocardial abscesses.[3,7,24] Left atrial mural endocarditis may also be acquired from the extension of a pulmonary abscess through a pulmonary vein.[25] In rare cases, vegetative

TABLE 1.—*Clinical and Pathologic Features of Reported Cases of* Aspergillus *Mural Endocarditis*

Source	Age	Sex	Underlying Disease	Predisposing Factors: Prior Antibiotic Therapy	Prior Corticosteroid Therapy	Prior Cytotoxic Therapy	Fever	Precordial Murmur	Blood Cultures	Site of Vegetation	Necropsy Finding, Myocardial Abscesses	Peripheral Embolization*
Cawley, 1947[9]	8 yr	♂	None apparent	Yes	No	No	Yes	...	...	Left ventricle	Yes	No
Welsh and Buchness, 1955[10]	18 yr	♂	Leukopenia; "interstitial pneumonia"	Yes	Yes	No	Yes	...	Neg	Right ventricle	Yes	No
Levy and Cohn, 1955[26]	24 yr	♀	?Acute myeloblastic leukemia	Yes	Yes	No	Yes	Yes	Neg	Left ventricle	Yes	No
Grcevic and Matthews, 1959[11]†	22 yr	♂	None apparent	Yes	No	No	Yes	...	Neg	...	Yes	No
Luke et al, 1963[12]	7 wk	♀	Prematurity; erythroblastosis fetalis	Yes	Yes	No	Yes	Yes	Pos	Both ventricles	Yes	No
Paradis and Roberts, 1963[13]	8 wk	♀	Prematurity; disseminated CMV infection	Yes	Yes	No	...	...	...	Left ventricle	Yes	No
Tan et al, 1966[14]	10 wk	♀	Thrombocytopenia; diarrhea	Yes	Yes	No	Yes	...	...	Right atrium, both ventricles	Yes	No
Buchbinder and Roberts, 1972[25]	27 yr	♂	Lymphosarcoma	...	...	Yes	Yes	Yes	Neg	Left atrium	No	No
Walsh and Hutchins, 1979[23]	52 yr	♂	Renal failure, colon adenocarcinoma	Yes	No	No	Yes	No	Neg	Left atrium, mitral valve ring	Yes	No
	59 yr	♂	Acute monocytic leukemia	Yes	Yes	Yes	Yes	No	Neg	Right atrium, left ventricle	Yes	No
	9 yr	♂	Fulminant hepatitis, renal failure	Yes	Yes	No	Yes	No	Neg	Left ventricle	Yes	No
	16 yr	♀	Leukemia; renal failure	Yes	Yes	Yes	Yes	No	Neg	Both ventricles	Yes	No
	29 yr	♀	Renal transplant rejection	Yes	Yes	Yes	Yes	No	Neg	Right atrium, both ventricles	Yes	No
Peterson et al, 1984[16]	36 yr	♂	Leukemia	Yes	Yes	No	Yes	Yes	Neg	Both atria and ventricles	Yes	Yes
Mullen et al, 1986[17]	29 yr	♀	Alcohol and intravenous drug abuse	Yes	Yes	No	Yes	No	Neg	Left ventricle	...	Yes
This report	42 yr	♀	Systemic lupus erythematosus	Yes	Yes	Yes	Yes	No	Neg	Left ventricle	...	Yes

CMV = cytomegalovirus, Neg = negative, Pos = positive

*As documented by surgical excision or autopsy
†Case 3

mural endocarditis may occur that mimics valvular endocarditis, as illustrated in this report.

Aspergillus species mural endocarditis was first reported by Cawley in 1947.[9] A literature search for subsequent cases is complicated by reports containing imprecise descriptions of mural lesions. Cases are included in this analysis if valvular vegetations were absent and dichotomously branching septate hyphae were seen microscopically or *Aspergillus* species were cultured from mural endocardial lesions.

On this basis, 15 cases of *Aspergillus* mural (nonvalvular) endocarditis have been previously reported.[9-14,16,17,23,25,26] The clinical and pathologic features of these cases and the case reported here are given in Table 1. All patients had had fever and prior antibiotic therapy. Myocardial abscesses were found in all cases (14/14) in which an autopsy was done, including one case in which "focal acute myocarditis" was described.[25] Prior corticosteroid administration and concomitant cytotoxic therapy were predisposing factors in 80% (12/15) and 31% (5/16) of cases, respectively. Precordial murmurs were noted in only 36% (4/11) of cases. A blood culture was positive in only one case (8%), in which it was reported as showing "no growth, with mold contamination" ten days before death.[12]

A high degree of suspicion is an important prerequisite to diagnosing *Aspergillus* mural endocarditis, and suspicion is warranted when an underlying disease is present or immunosuppressive therapy has been given (Table 1). The specific diagnosis of mural endocarditis may be important to establish in that it suggests the presence of myocardial abscesses. Factors that may predispose to *Aspergillus* infection have been enumerated.[1-5,7,14,27] In a series of 98 cases of aspergillosis, Young and associates reported that 97% had an underlying predisposing condition, 85% had received chemotherapy, 70% had granulocytopenia, 87% had had corticosteroid therapy, and 97% had received antibiotics.[3]

An antemortem diagnosis of *Aspergillus* endocarditis is rarely made. Negative blood cultures and serologic studies, both encountered in the present case, are well described in this setting. The 8% blood culture yield reported herein is consistent with previous yields of 8% and 11% in two large series of *Aspergillus* endocarditis.[4,7] In the 98 cases of aspergillosis described by Young and colleagues, none showed a positive blood culture.[3] This low frequency has been attributed to fungemia that is intermittent and circulating hyphae too large to traverse systemic capillaries.[4,7] Serology has also been of dubious diagnostic value,[28] although seroconversion, if documented, has been associated with increased survival in disseminated aspergillosis.[27]

M-mode and two-dimensional echocardiography has been of diagnostic and prognostic value in bacterial[29,30] and fungal[31,32] endocarditis. Due to the larger size of vegetations seen in cases of fungal endocarditis, greater sensitivity with echocardiography would be expected. Although Dillon and co-workers reported being able to visualize masses of 2 mm or greater,[33] the 5-mm mural vegetation in our patient was not seen. Peterson and colleagues have reported echocardiographic nonvisualization of four-chamber *Aspergillus* endocarditis and myocarditis, with a postmortem examination revealing mural vegetations as large as 1 cm in diameter.[16] Factors other than size that may explain nonvisualization include location, configuration, and acoustic properties.[34] More recently, Mullen and associates have reported serial echocardiographic visualization of an *Aspergillus* mural endocardial mass measuring 4 by 2 cm.[17] The identification of this mass led to an appropriate surgical excision with continued antifungal chemotherapy; death ensued in this case, however, despite the antemortem diagnosis.

Aspergillus infection limited to mural endocardium has been less commonly reported than *Aspergillus* valvular endocarditis, for which more extensive experience indicates aggressive therapy is desirable. Following echocardiographic confirmation of the diagnosis,[30,32] the optimal management entails early valve replacement and prolonged antifungal chemotherapy.[4,6-8] Cures have been reported with this combined approach[35-37] and with surgical treatment alone.[38,39] Survival without valve replacement has not been described.

Aspergillus mural endocarditis has been uniformly fatal. Despite achieving an antemortem diagnosis in this case at cardiotomy, and in a recent report by serial echocardiography,[17] cure did not result. Earlier recognition of this process permitting an earlier initiation of aggressive therapy may be required for a successful outcome.

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Alopecia Universalis as a Feature of Polyglandular Autoimmunity Type I

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THE OCCURRENCE of two or more endocrine diseases in the same patient has been noted since the 19th century.[1] Numerous workers have described an association of multiple autoimmune diseases of the endocrine organs, including the adrenal glands, endocrine pancreas, thyroid, parathyroid, and ovaries. These endocrine disorders are frequently associated with other disorders of tissue-specific autoimmunity, such as pernicious anemia, vitiligo, and alopecia.

These polyglandular autoimmunity (PGA) syndromes have been classified into two major types, based on familial clustering.[2,3] Type I manifests at least two features from the triad of Addison's disease, hypoparathyroidism, and chronic mucocutaneous candidiasis. Type II is present in patients who have Addison's disease with autoimmune thyroid disease or insulin-dependent diabetes mellitus, or both, but who do not have hypoparathyroidism or candidiasis. Associated immune disorders other than hypoparathyroidism and candidiasis may also be present with either type.

We report here the case of a patient who had the added feature of alopecia universalis as a manifestation of her type I polyglandular autoimmunity syndrome. Although alopecia areata is frequent in patients with the type I form,[2] alopecia universalis is rare. Alopecia universalis was one of the most striking features in our patient, contributing greatly to her morbidity by exacerbating her emotional instability.

(Imam K, Abdullah M, Felicetta JV: Alopecia universalis as a feature of polyglandular autoimmunity type I. West J Med 1988 Sep; 149:338-341)

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
FSH = follicle-stimulating hormone
HLA = human leukocyte antigen
LH = luteinizing hormone
PGA = polyglandular autoimmunity
PTH = parathyroid hormone

Report of a Case

The patient initially presented to Detroit Children's Hospital in 1962 at age 3 with a history of generalized seizures for one month and a chronic fungal infection of the nails. Laboratory studies at that time showed a serum calcium level of 4.4 mg per dl and a phosphorus of 13.5 mg per dl. A diagnosis of primary hypoparathyroidism was made on the basis of a pronounced phosphaturic response to the intravenous administration of parathyroid hormone and a return to normal of calcium and phosphorus levels after giving the hormone. An adrenocorticotropic hormone (ACTH) stimulation test (cosyntropin test) reportedly showed an appropriate rise in the urinary cortisol level. Therapy was initiated with elemental calcium and vitamin D.

She did well initially except for the progressive development of alopecia areata beginning at age 5. This had progressed to alopecia universalis by age 8, and she always wore a wig after that time. According to her parents, emotional instability of increasing severity first became manifest at the time she began wearing the hairpiece. The diagnosis of hypoparathyroidism was confirmed at Grace Hospital in Detroit in 1979 when she was 20. At that time a C-terminal parathyroid hormone (PTH) level was less than 150 pg per dl (normal 197 to 315), with a simultaneous serum calcium level of 6.4 mg per dl (normal 8.8 to 10.0) and an ionized calcium of 2.56 mg per dl (normal 3.7 to 4.5). An 8 AM plasma cortisol level was 10 μg per dl, a 4 PM cortisol level 8.7 μg per dl, thyroxine 9.8 mg per dl, triiodothyronine resin uptake 40%, follicle-stimulating hormone (FSH) 12 mIU per ml, and luteinizing hormone (LH) 66 mIU per ml. Calcium supplementation and vitamin D therapy were continued.

At age 23, she presented to a North Carolina hospital with nausea, vomiting, weakness, dizziness, salt craving, increasing skin pigmentation, and an 18-kg (40-lb) weight loss over three months. Her blood pressure was 80/40 mm of mercury. Her serum calcium level was 6.5 mg per dl; an 8 AM cortisol level was undetectable. An intravenous ACTH stimulation test elicited values of less than 1 μg per dl at baseline, 30 minutes, and 60 minutes. Her baseline ACTH level was more than 250 pg per ml (normal 20 to 100). A computed tomographic scan of the head revealed bilateral basal ganglia calcification, consistent with hypoparathyroidism. A regimen of calcium carbonate; calcitriol, 0.5 μg daily; and cortisone acetate, 37.5 mg daily in divided doses, was started.

She was first admitted to Wayne County General Hospital in Detroit in December 1981 because of profound somnolence and weakness. According to her boyfriend, she had been extremely sporadic in taking her medications. She had also been experiencing considerable emotional stress related to her alopecia universalis and had noted intermittent amenorrhea and irregular menstrual cycles for more than two

TABLE 1.—*Manifestations of the Polyglandular Autoimmunity Syndrome Type I in a Female Patient and Her Brothers*

Feature of Syndrome	*Index Patient Born 1958*	*1st Brother Born 1961*	*2nd Brother Born 1970*
Hypoparathyroidism	Onset age 3½ yr	Onset age 8 yr	Onset age 4½ yr
Addison's disease	Onset age 23 yr	Onset age 16 yr	Onset age 11 yr
Mucocutaneous candidiasis	Yes	Yes	Yes
Vitiligo	Yes	No	Yes
Alopecia	Universalis	Areata	No

years. Her blood pressure while supine was 88/56 mm of mercury with a pulse of 102 per minute, and while sitting 76/54 mm of mercury with a pulse of 120 per minute. Her temperature was 36°C (97°F). Abnormal physical findings were limited to skin hyperpigmentation, onychomycosis of the fingernails, cheilosis, oral mucosal candidiasis, and alopecia universalis. The family history revealed that two living brothers also manifested the type I syndrome, as shown in Table 1. Two sisters, aged 29 and 23, had no history of endocrinopathy; her mother, aged 47, and her father, aged 48, were also said to be free of any endocrine pathologic disorder.

A laboratory evaluation elicited the following values: sodium 129, potassium 4.6, and carbon dioxide 18 mEq per liter; creatinine 1.2, glucose 27, calcium 8.0, and phosphorus 5.9 mg per dl; PTH 0.8 pg per ml (normal 1.97 to 3.15); cortisol 2.5 μg per dl; immunoglobulin A 128 mg per dl (normal 75 to 312); normal thyroid function values; FSH 8 and LH 10 mIU per ml.

After initial therapy with intravenous hydrocortisone, she was placed on a maintenance regimen of hydrocortisone, 30 mg a day in divided doses; calcium carbonate; dihydrotachysterol (Hytakerol), 0.25 μg three times a day; and ketoconazole, 200 mg a day. Although we did not look for organ-specific antibodies, we presumed that the Addison's disease and hypoparathyroidism were on an autoimmune basis.

The patient was lost to follow-up until March 1983, when she presented with seizures and a blood glucose level of 30 mg per dl. She again admitted to noncompliance with her medications, as well as depression related to her alopecia. She had similar admissions in May, September, and October 1983. On each occasion noncompliance led to hypoglycemia, hypocalcemia, seizures, and hypotension.

In mid-December 1983, the patient was unexpectedly found dead in a friend's apartment. Once again the history of noncompliance was obtained. Vitreous fluid chemistry tests done 30 hours postmortem revealed a potassium level of 10.1 mEq per liter, a calcium of 6.0 mg per dl, and a blood cortisol level of only 0.2 μg per dl. Vitreous fluid chemistry levels are thought to correlate closely with blood levels at the time of death.

On postmortem examination there was an enlarged pituitary gland with hypertrophy of the basophilic and chromophobic cells. The parathyroid glands could not be identified, while the adrenal glands showed substantial atrophy and total replacement of the cortex by fibrous tissue. On microscopic examination there were scattered chronic inflammatory cells, primarily lymphocytes, within the dense cortical stroma (Figure 1). The adrenal medulla consisted of normal cells without atrophy or hypertrophy. The ovaries contained few developing follicles and only rare scattered oogonia. Chronic inflammatory infiltrate consisting of lymphocytes and plasma cells was found throughout the ovarian cortex, and no corpora albicantia were seen. Neither the thyroid nor the pancreatic islets showed any abnormalities.

Discussion

Sporadic cases of associated endocrinopathies and dermatologic disorders have been reported over the years. Thorpe and Handley reported in 1929 an association between hypoparathyroidism and chronic mycelial stomatitis.[4] Talbot and co-workers were the first to describe (in 1943) the association between Addison's disease, mucocutaneous candidiasis, and superimposed hypoparathyroidism.[5] In 1954 Papadatos and Klein reported the additional association of alopecia areata in patients with Addison's disease and hypoparathyroidism.[6] The full triad of familial juvenile hypoadrenocorticism, hypoparathyroidism, and superficial moniliasis was again reported by Whitaker and associates in 1956.[7] They suggested that the superficial moniliasis was the result of dystrophic lesions of the mucosa, skin, and nails due to hypoparathyroidism. Our patient apparently is the first to have alopecia universalis as a feature of the polyglandular autoimmunity syndrome type I.

Sutphin and colleagues in 1943 were the first to suggest a hereditary component to the PGA syndrome.[8] The first genetic study, however, was not reported until 1968, when Spinner and co-workers concluded that PGA type I is inherited as an autosomal recessive trait. They noted that the age of onset is young and that male and female patients are affected in equal numbers.[9] Because the aggregation within siblings involves both sexes, Eisenbarth and associates have suggested an autosomal recessive inheritance.[10] The type I syndrome is not human leukocyte antigen (HLA)-associated

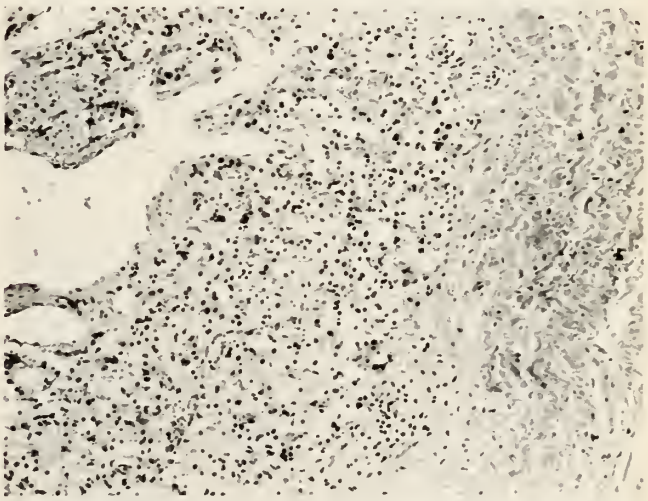

Figure 1.—Adrenal gland shows normal medullary tissue (left side) and dense cortical stromal replacement of the cortex (right side). Viable cortical cells were not identified. Scattered lymphocytic cells are present within the fibrous tissue replacing the cortex (original magnification × 300).

at a population level,[11] nor does it correlate with HLA inheritance in involved families.[12] This is in contrast to the type II PGA syndrome, which appears to be linked to the HLA system and especially to the inheritance of the HLA-B8 (Dw3) haplotype.

An autoimmune basis for the polyglandular syndromes was first suggested by Williams and Wood in 1957.[13] Wuepper and Fudenberg have also presented evidence of faulty immunologic responsiveness.[14] They found organ-specific antibodies in a patient with mucocutaneous moniliasis and multisystem endocrine diseases, and they identified similar antibodies in 17 members of the patient's family. Castells and co-workers have also shown defective delayed hypersensitivity in three siblings with mucocutaneous candidiasis, decreased adrenal reserve, and hypoparathyroidism.[15]

Recent reports suggest that patients with the type I PGA syndrome have an underlying defect in cell-mediated, thymus-derived (T-lymphocyte) immunity.[16,17] Arulanatham and colleagues reported that suppressor T-lymphocyte functions are defective in such patients.[18] Delayed hypersensitivity by skin testing is commonly defective in those with chronic mucocutaneous candidiasis. The frequent observation of IgA deficiency in type I PGA is also in keeping with an abnormality in thymic function. Attempts at thymus transplantation have led to some clinical improvement,[19,20] and the use of a transfer factor coupled with amphotericin B has afforded considerable improvement in some patients with chronic mucocutaneous candidiasis.[21] These findings incriminate the thymus as the defective organ in the type I PGA syndrome.

The type I PGA syndrome is characteristically recognized clinically in early childhood. Chronic mucocutaneous candidiasis often occurs first with accompanying hypoparathyroidism, followed later by adrenal insufficiency.[2] Decades may elapse in between the diagnosis of one disease and the onset of another. The peak age of onset of Addison's disease, however, is before 10 years. Within a given kinship, some persons may express only one or two of the three manifestations of the type I syndrome.[2] In the family presented here, the age at which Addison's disease began ranged between 11 and 23 years (mean, 16.7 years) and for hypoparathyroidism between 3½ and 8 years (mean, 5.3 years).

In addition to her classic type I triad, our patient also had intermittent amenorrhea and oligomenorrhea. Her ovarian findings at autopsy were consistent with the recent report by Gloor and Hurlimann[22] and the previous study by Irvine and Barnes[1] in which more than 25% of patients with idiopathic Addison's disease had premature gonadal failure with increased levels of gonadotropins.

Our patient suffered from severe psychiatric disturbances that contributed significantly to noncompliance with her medication regimen. Her psychiatric disturbances were probably multifactorial. One factor was a low self-esteem and an extremely poor body image related to her alopecia universalis. A second factor, however, may have been hypoparathyroidism. Denko and Kaelbling report that the mental disturbances associated with hypoparathyroidism may include intellectual impairment, organic brain syndrome, functional psychosis, pseudoneuroses (hysteric, hypochondriacal), and nonspecific symptoms such as depression and nervousness.[23] A third etiologic factor could have been her Addison's disease. The mental disorders associated with Addison's disease include apathy, somnolence, insomnia, troublesome dreams, and dulling of the intellect.[24] Indeed, Thomas Addison himself noted that as Addison's disease progresses, the mind frequently wanders. His first patient, a man, had a childish demeanor and spoke with an "intolerable whine."[25]

The immediate cause of death in our patient was clearly noncompliance with her medical regimen. Fraser and Clark have managed a similar patient with Addison's disease and autoimmune hypothyroidism with nurse-supervised therapy, using a regimen of oral thyroxine weekly, intramuscular methylprednisolone weekly, and intramuscular deoxycortisone pivalate monthly.[26] Such an approach might have prolonged our patient's survival.

Our patient's disease was aggravated and her death partially related to the emotional stress of her alopecia universalis. Alopecia of this severity is never a trivial disorder. In addition to its cosmetic significance, alopecia universalis has the potential to create or to exacerbate psychiatric disease.

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Reversal of Severe Osteopenia in a Patient With Hyperprolactinemia Treated With Bromocriptine

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HYPERPROLACTINEMIA IS OFTEN due to a prolactin-secreting pituitary adenoma or to idiopathic hypersecretion of prolactin. Since 1971 when prolactin was distinguished from growth hormone,[1] hyperprolactinemia has been found to be a common condition. It is seen in 15% to 30%[1-3] of cases of amenorrhea and 60% to 70% of all tumors previously thought to be functionless.[4]

Initially the clinical effects of hyperprolactinemia were believed to be mainly galactorrhea, infertility, and amenorrhea. More recently, hyperprolactinemic patients have shown decreased bone mineral content by single-photon measurement of radial bone mineral, by computed tomographic measurement of vertebral bone mineral, and by dual-photon measurements of the vertebral bone mineral.[2,3,5,6] Osteopenia has also occurred in men with hyperprolactinemia.[7,8] Increased radial bone mineral content in hyperprolactinemic women on therapy with bromocriptine was recently reported.[9] Increased spinal bone mineral content by quantitative computed tomography also has been reported by Schlechte and co-workers.[10]

We report the case of a 48-year-old woman with persistent hyperprolactinemia and idiopathic hypercalciuria concurrent with severe radial and lumbar spine osteopenia who had reversal of the spinal osteopenia by long-term bromocriptine therapy. The reversal was documented by serial dual-photon absorptiometry.

(Lindberg JS, Kolb FO, Blau RA, et al: Reversal of severe osteopenia in a patient with hyperprolactinemia treated with bromocriptine. West J Med 1988 Sep; 149:341-343)

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Report of a Case

A 45-year-old nulliparous woman presented with a 14-year history of amenorrhea and galactorrhea that began after a miscarriage. At age 36, sellar tomography and a pneumoencephalogram were normal. A year later, an elevated prolactin level of 330 ng per ml (normal less than 23) was found, and repeat sellar tomography showed anterior, inferior, and posteroinferior sellar erosion. Amenorrhea, galactorrhea, fatigue, and mild obesity persisted, but she had no vision complaints, and the findings of a general physical examination were normal. Osteoporosis and scoliosis were noted on a chest roentgenogram. She underwent transsphenoidal exploration of the pituitary gland. No evidence of adenoma was found at operation, and a biopsy revealed normal pituitary tissue. The patient was treated briefly with a regimen of bromocriptine mesylate after her operation.

She was not seen again until November 1984 when, at age 45, she reported persistent fatigue, galactorrhea, amenorrhea, and back pain. Multiple rib fractures and a compression fracture of the seventh thoracic vertebra were seen on plain films of her chest. These had occurred in spite of her intermittent use—missing five to ten days of medication every six months—of 0.625 mg of conjugated estrogens daily with cyclic doses of 10 mg of progesterone, which caused withdrawal bleeding, plus 1 gram of calcium carbonate per day over several years. She had a history of hypothyroidism treated with the administration of 0.15 mg of liotrix (Thyrolar-2) daily. Her family history was remarkable only for nephrolithiasis in a cousin.

The patient weighed 74 kg (178 lb), was 158 cm (62¼ in) tall, and had an arm span of 165 cm (65 in). Galactorrhea was inducible with breast manipulation. Visual fields were normal. Serum electrolytes and hemogram values were normal. A serum calcium level was 10 mg per dl and phosphate was 3 mg per dl, both values being within the normal range. A prolactin level was 495 ng per ml (normal 2 to 20). An intact parathyroid hormone level was 19 pg per ml, and the 25-hydroxyvitamin D level was 38 ng per ml, both being within normal limits. The urine calcium content was 332 mg per 24 hours (normal 50 to 250), and creatinine, uric acid, and 24-hour urine phosphate levels were normal.

Postsurgical sellar changes were seen on a computed tomographic scan of the head and neck, but the pituitary gland was considered to be normal and without evidence of adenoma. The patient's radial bone density in the "cortical area" at the junction of the distal and middle thirds was 0.65 grams per cm, 3.37 standard deviations (SD) below the mean for women aged 40 to 49 years.[11] Her spinal bone mineral measurement of the second through the fourth lumbar vertebrae was 0.77 grams per cm^2, 3.67 SD below the mean for women aged 40 to 49 years (see Table 1).[12]

In January 1984, bromocriptine mesylate, 5 mg a day, and 50 mg of triamterene and 25 mg of hydrochlorothiazide were added to her long-term cyclic therapy with conjugated estrogens and medroxyprogesterone acetate plus calcium carbonate. The patient had regular withdrawal menstruation. Her prolactin level decreased from 400 ng per ml to 83 ng per ml on a regimen of 7.5 mg of bromocriptine mesylate per day. After increasing the dose to 10 mg a day, her prolactin level was reduced to 37 ng per ml. A repeat spine mineral assessment by dual-photon absorptiometry showed an increased density of 29%, going from 0.770 grams per cm^2 in December 1983 to 0.997 grams per cm^2 12 months later

TABLE 1.—*Serial Bone Absorptiometry in a Woman With Hyperprolactinemia Treated With Bromocriptine Mesylate*

Patient Variable	*12/5/83*	*12/13/84*	*2/6/86*	*2/27/87*	*5/18/87*
Age, yr	46	47	48	49	50
Prolactin level, ng/ml	495	83	37	200	140
Bromocriptine dose, mg	0	7.5	10.5	12.5*	10
Cortical area of radius					
Width, cm	1.20	1.20	1.283	...	...
Density, grams/cm	0.65	0.66	0.689	...	...
Lumbar spine					
L2-4, grams/cm^2	0.770	0.997	1.124	0.988	...
Hip					
Femoral neck, grams/cm^2	...	..	..	0.80	...
Ward's triangle, grams/cm^2	...	..	..	0.54	...
Trochanter, grams/cm^2	...	..	..	0.71	...

*Patient was noncompliant at this time.

(Figure 1; Table 1). A year after this measurement, her bone mineral content of the second through the fourth lumbar vertebrae had further increased 13% to 1.124 grams per cm^2, for a total increase of 46% in two years of therapy. Her radial mineral content increased by 6% over two years. The coefficient of variation in this laboratory for short-term measurements is less than 2% for both spine and radius measurements. The long-term coefficient of variation for both measurements in our laboratory is 2.5% for the spine and 2% for the radius.

The patient then had an increased sense of well-being and has had no further stress or compression fractures. Because of persistent hypercalciuria (547 mg per 24 hours), a regimen of 100 mg of triamterene and 50 mg of hydrochlorothiazide was started. At a dose of 150 mg of triamterene and 100 mg of hydrochlorothiazide per day, her urinary calcium content returned to normal—250 mg per 24 hours. Finally, in April of 1986, on a magnetic resonance imaging study, a 12-mm macroadenoma was depicted in the posterior aspect of the sella, as was erosion of the left half of the dorsum sella. A year later, after taking her medication irregularly, the prolactin level again rose to 200 ng per ml, and her urinary calcium level increased to 408 mg per 24 hours. Repeat bone mineral measurements of her spine showed a decrease from 1.121 to 0.998 grams per cm^2, or a loss of 12%. The hip bone mineral was measured for the first time at this point and also showed mineral loss at two of three sites, with the femoral neck 0.6 SD below the normal mean for a woman of her age, the Ward's triangle 1.8 SD below, and the trochanteric area 0.2 SD above.[12]

Discussion

This patient presented with an interesting problem of persistent hyperprolactinemia, severe idiopathic hypercalciuria, and progressive bone loss despite having had a negative transsphenoidal exploration eight years earlier and a four-year history of intermittent therapy with conjugated estrogens, progesterone, and calcium supplementation. Concomitant treatment of her hyperprolactinemia with bromocriptine mesylate, as much as 10 mg a day, and of her hypercalciuria with triamterene and hydrochlorothiazide increased her lumbar spine mineral content by a total of 46% in 26 months.

The mechanism by which hyperprolactinemia causes osteopenia is not clear. Bohnet and colleagues and Jacobs and associates reported estradiol levels consistent with an early follicular phase or postmenopausal levels in hyperprolactinemic women.[13,14] Klibanski and co-workers found low estradiol levels comparable to an early follicular phase or postmenopausal levels in 14 hyperprolactinemic patients[2] and also found a positive correlation between low bone mineral content, as measured by single-photon absorptiometry of the radius, and low estradiol levels. They postulate that estrogen deficiency is directly or indirectly responsible for osteopenia. Jackson and associates thought the low testosterone level noted in a male patient with hyperprolactinemia to be the cause of the osteoporosis they observed by single-photon absorptiometry and by bone biopsy.[8] This is in contrast to the findings by Schlechte and colleagues, who also used single-photon absorptiometry to measure the radial bone mineral content in patients with prolactin-secreting tumors two to five years after transsphenoidal operations.[5] These authors compared bone mineral content in patients with transsphenoidal surgical "cures" and "noncures" and in amenorrheic normoprolactinemic women and found that women with prolactin-secreting pituitary tumors had significantly decreased bone density, regardless of surgical outcome, when compared with eumenorrheic and amenorrheic normoprolactinemic controls. There was no correlation between low estradiol levels and decreased bone density, except in patients with persistent hyperprolactinemia. In a more recent report, Schlechte and co-workers showed little improvement in forearm bone measurements but increased trabecular bone mineral content measured by quantitative computed tomography in successfully treated patients with hyperprolactinemia.[10] The successfully treated patients, however, still showed diminished spinal mineral content when compared with normal persons, suggesting that factors other than the prolactin and estradiol levels account for the osteopenia.

Subsequently, Koppelman and colleagues assessed the effect of prolactin by using computed tomographic measurement of vertebral bone mineral content in hyperprolactinemic women compared with age-matched controls.[6] This was in contrast to previously reported studies wherein single-photon absorptiometry, which predominantly measures cortical bone, had been used. They found that trabecular bone mineral content was modestly but significantly reduced in hyperprolactinemic women compared with closely matched normal women. There was no correlation between decreased bone mineral content and estrogen levels in their study patients. In none of these studies were significant dif-

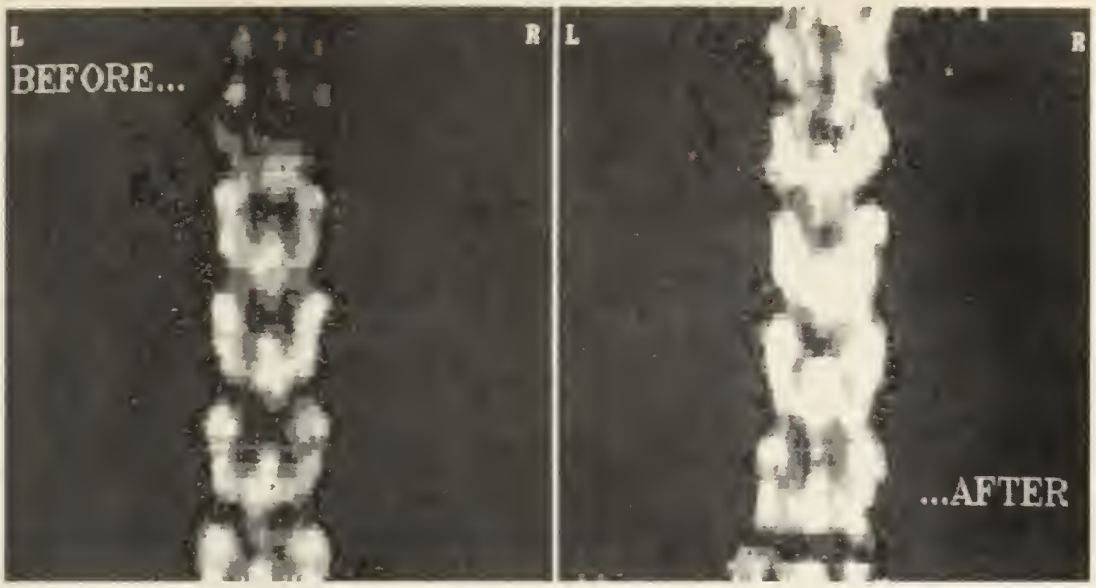

Figure 1.—Transmission scans show the lumbar spine before and after one year of treatment with bromocriptine mesylate and thiazide. The 29% increase in bone mineral content is easily apparent as an increase in whiteness that is proportional to the density of the measured vertebral segments. These photographs were taken from a single video display showing identically processed data.

ferences found between levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, parathyroid hormone, phosphate, or calcium; other studies, however, have shown a slight increase in 1,25-dihydroxyvitamin D levels in hyperprolactinemic women.[15,16]

The findings in our patient in whom progressive osteopenia developed despite estrogen replacement and in other reports of conflicting data regarding the correlation of estrogen levels and bone mineral content in hyperprolactinemic women suggest that factors other than estrogen may be important in bone loss in hyperprolactinemic patients. In our patient, idiopathic hypercalciuria likely contributed to her osteopenia. It has been postulated that prolactin may act directly on bone to cause bone loss[17] or that there may be a relationship between the central dopaminergic system and mineral homeostasis.[18,19] Another possibility is that hyperprolactinemia causes end-organ resistance to both endogenous and exogenous estrogens, which could lead to bone loss, similar to the resistance to both endogenous and exogenous testosterone in men with hyperprolactinemia.[7,20]

Through the use of single-photon absorptiometry measurement, other authors have also shown bone mineral content to be significantly increased in hyperprolactinemic women treated with bromocriptine mesylate, surgical intervention, or both.[7,9,18] This bone mineral content increase was accompanied by a significant decrease in prolactin levels. Schlechte and colleagues also found improvement only in spinal trabecular bone mass measured by quantitative computed tomography in treated patients.[10]

Conclusion

The mechanism of the osteopenia concurrent with hyperprolactinemia is not clear, but, as shown in our patient, it can be reversed by restoring the prolactin level to normal. The hypercalciuria in this patient most likely contributed to her osteopenia. It might have been related to the hyperprolactinemia itself by a mechanism not yet defined, or it might have been due to idiopathic hypercalciuria. Because of the reversible osteopenia in our patient and reported in other cases of hyperprolactinemia, we advise measuring the spine mineral content in asymptomatic patients with elevated prolactin levels and then, in those patients who show osteopenia, treating with a pituitary operation or the administration of bromocriptine mesylate, or both.

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Correspondence

Group G Streptococcal Bacteremia With Presumed Endocarditis in a Patient With AIDS

To the Editor: Although still relatively uncommon, serious infections due to group G streptococci have been recognized with increased frequency.[1,2] Bacteremia and endocarditis have occurred almost exclusively in immunocompromised patients, including those with malignant tumors or other chronic diseases, alcoholism, drug addiction, and the elderly. We would like to bring to the attention of the readers of the journal a case of group G streptococcal bacteremia with presumed endocarditis in a patient with the acquired immunodeficiency syndrome (AIDS), an association that to our knowledge has not been reported previously.

A 37-year-old gay man with a history of intravenous drug abuse, Kaposi's sarcoma, and antibody to HIV was admitted to hospital for evaluation of fever and back pain for three days. He appeared to be chronically ill. His temperature was 39.3°C (102.7°F). Roth's spots were seen in both fundi oculi. He had poor dentition, with multiple caries and gingivitis. Heart sounds were normal, and no murmurs were heard. The lungs and abdomen were normal. He had no spinal tenderness. He had a swollen and tender left metacarpophalangeal joint, but no splinter hemorrhages, Osler's nodes, or Janeway's lesions, were seen. A purple lesion measuring 1 × 1 cm was present on the left knee. His hematocrit was 33.3% and the leukocyte count 7,100 per μl. A chest x-ray film was clear. His urine contained no erythrocytes.

The patient was presumed to have infective endocarditis and was treated empirically with nafcillin. Three sets of blood cultures were positive for group G streptococcus. The antibiotic therapy was changed to penicillin G. An echocardiogram showed normal valve function with no vegetations. The patient's fever abated, and his back pain disappeared over the next several days. The results of a repeat echocardiogram seven days after admission were unchanged. A bone scan was normal.

The most common source for group G streptococcal bacteremia is infection of the skin or soft tissue. In our patient, the inflamed gingivae may have served as the entry site, although infection due to intravenous drug abuse was also possible. Endocarditis is the most commonly reported clinical syndrome associated with group G streptococcal bacteremia, and vegetations on heart valves are often not detected by echocardiogram.[1] Our patient was presumed to have endocarditis, a diagnosis supported by the finding of Roth's spots in both eyes and arthritis of one metacarpophalangeal joint.

In addition to the better-known CD4 lymphocyte defects in AIDS, B-cell function is also impaired, and a diminished response to protein and polysaccharide vaccines has been documented.[3] Bacteremia due to *Streptococcus pneumoniae, Haemophilus influenzae,* and other streptococci has been shown to occur more frequently than predicted in AIDS patients.[4,5] This same immunologic dysfunction may have permitted the establishment of group G streptococcal bacteremia in our patient. The tendency of group G streptococci to infect immunocompromised patients makes it surprising that severe infection has not been reported more frequently in AIDS patients.

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Angiography and Polyarteritis Nodosa

To the Editor: In the March 1988 Radiologic Case by Ohmart and associates on the angiographic manifestations of polyarteritis nodosa,[1] the authors state that "involvement of the hepatic arteries only occurs in patients who are seropositive for the hepatitis B surface antigen." Travers and coworkers noted, however, that there was no correlation between the angiographic findings of microaneurysms in the hepatic circulation and the clinical finding of liver disease or the laboratory finding of hepatitis B surface antigen.[2] Although studying only a small number of patients, these authors also noted that the frequency of aneurysms in the hepatic circulation was higher than that found in the renal or mesenteric vascular beds. As noted by Ohmart and colleagues, there is no specific laboratory test for the diagnosis of polyarteritis nodosa. This includes the finding of microaneurysms on angiography, since other disorders can cause this, including bacterial endocarditis, systemic lupus erythematosus, Wegener's granulomatosis, and, in a report by Easterbrook,[3] tumor (in a young woman with poorly differentiated metastatic Wilms's tumor).

Although it has been suggested that the finding of aneurysms on angiography denotes a poorer prognosis for patients with polyarteritis nodosa,[4] this has not been confirmed by other studies. Thus, the angiographic diagnosis should certainly be supported by the clinical pattern as well as with tissue diagnosis wherever possible. When an angiographic diagnosis is attempted, studies in multiple vascular beds may be necessary to make the diagnosis, and the clinical or laboratory presence of specific visceral involvement apparently cannot be predicted by the angiographic findings.

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Suction-Assisted Lipectomy

To THE EDITOR: This is in response to an editorial, "Suction-Assisted Lipectomy—Caveat Emptor," in the June 1988 issue.[1]

The statements made by the two authors of this editorial deserve comment, particularly Dr Simon Fredricks, who was responsible for a study by the American Society of Plastic and Reconstructive Surgeons of morbidity and mortality from suction lipectomy, which was released to the press in October 1987.

The suggestion is made that only surgeons who have general surgical experience are competent to do liposuction.

It is my judgment that this is errant nonsense. In close questioning of Dr Fredricks, I discovered that of 11 deaths reported in that study, 9 were produced by either plastic surgeons, obstetricians, or ear, nose, and throat doctors, all of whom had had general surgical training. It was his allegation that in one case of death following liposuction done by a dermatologist, death was due to an anesthesiologist's error, not the dermatologist's.

It is difficult for me to see how Dr Fredricks can suggest that this procedure, which has been nurtured and developed by dermatologists, should only be in the province of those who have the imprimatur of his organization.

I think the journal would have been better served if it had obtained a more balanced reaction to the scientific article, "Fasciitis and Abscesses Complicating Liposuction,"[2] from dermatologic surgeons who have had broad experience in this matter.

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Emergency Physicians and Preventive Medicine

To THE EDITOR: Emergency physicians are often the only primary care providers seen by many patients. As a consequence, it may behoove them to be familiar with and practice preventive medicine.

In order to assess attitudes and practices concerning preventive cardiovascular medicine, we sent a survey to 86 emergency physicians in Utah. Questions were asked regarding the common risk factors for cardiovascular disease (CVD): cholesterol, smoking, hypertension, positive family history, and sedentary life-style. Respondents were asked their opinions and practices regarding patient education and management, as well as what they did to reduce their own risk for CVD. Of those polled, 48 (56%) responded.

With respect to cholesterol, 98% thought that lowering serum cholesterol would lower CVD risk, and 96% would begin therapy at levels as low as 220 mg per dl. Only 56%, however, knew their own serum cholesterol level. Of these, only three had levels that would be considered significantly elevated for their age groups. Almost all (93%) reported some personal reduction in fat and cholesterol intake over the last 10 years; many claimed a reduction greater than 50%.

Virtually all emergency physicians polled thought that quitting smoking would decrease the risk of CVD, and most felt that counseling in the emergency department would have some positive effect. On the other hand, 20% thought that patients would not comply with physician recommendations to stop smoking, and a corresponding 23% made no effort to counsel their last patient who smoked. Only two of the physician respondents smoked, and although both felt intervention in the emergency department was worth attempting, only one believed patients would stop because of it.

In general, respondents were much more aggressive with high blood pressure, with 90% recommending at least dietary changes and exercise to their last hypertensive patient. Most also referred such patients to another physician for follow-up. Only one physician had a blood pressure above 140/90 and was not taking antihypertensive medication.

As a negative risk factor, exercise was thought by more than 90% of physician respondents to effect favorable changes in blood pressure and serum high-density lipoprotein levels, and 94% thought some patients would comply with exercise recommendations. Of the respondents, 54% exercised at least three times per week, while 12% did not exercise at all.

Respondents who had a positive personal or family history of CVD were generally more aggressive in their views, personal practices, and recommendations than those without such backgrounds. Of the respondents, 75% were younger than 45—before the age when most CVD complications are manifest. Nonetheless, most appeared to be in good health and to have taken steps to minimize their own CVD risk factors. To a fair degree, these attitudes carry over into their emergency department practices, in that most attempt to educate and refer patients who are at risk for CVD. We feel, however, that there is room for improvement. This might be accomplished by the teaching of preventive cardiovascular medicine concepts in emergency medicine continuing medical education and residency training programs.

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Gastroesophageal Reflux

To THE EDITOR: An article[1] and an editorial[2] in the July issue review the diagnosis and treatment of gastroesophageal reflux and its often unsuspected complications. Although Dr Ward and associates[1] mention that patients should be advised to eat early, eat less, avoid spicy foods, alcohol, coffee, and tobacco, there is no real discussion of the *cause* of gastroesophageal reflux.

The interns in my class (Letterman Army Hospital, San Francisco, 1954) gained a reputation for being good diagnosticians. Among ourselves we knew a large part of our success was due to the immediate identification of patients we called CATs—people who lived on coffee, alcohol, and tobacco. In our minds, the coffee–alcohol–tobacco syndrome consisted of dyspepsia, obesity, chronic cough, hoarseness, anosmia, chronic fatigue, impaired libido, and "bad teeth."

It is too easy for physicians to tell patients to eat right, cut down on coffee, and stop smoking and drinking. The patient will usually follow such advice for a short time, but in most cases will soon return to these "bad habits," feeling more weak and worthless than before. Psychiatry is of little benefit for the very reason that nothing is wrong, necessarily, with the patient's mind or personality.

The problem is an immense societal one, apparently deeply interwoven with this country's tenets and goals. Practitioners of preventive medicine, nutritionists, and health educators long ago learned that the negative approach—"Don't smoke because you'll get cancer, emphysema, gastroesophageal reflux, and die of a heart attack"—has little lasting impact. The successful, positive approach—"Live healthy, live happy, live free, keep fit, love well, and feel good"—espoused by all sorts of non-medical motivational modalities, as well as most frontline medical practitioners, gives us hope that future generations might not be afflicted with a 30% to 40% prevalence of gastroesophageal reflux and related problems.

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An Unusual Complication of Diabetes

To THE EDITOR: A 55-year-old Native American man, somewhat obese, came to my office because, one week before, he had caught his penis in his zipper and torn the skin. He was concerned because it seemed slow to heal. He had little medical history and rarely sought medical advice. The skin on the distal half of the penis was found on examination to be shiny and fragile, with numerous small tears.

Some mumbled advice about vitamin E cream was already underway when my further examination revealed some areas of brownish discoloration around his ankles, which he admitted were somewhat pruritic. A dipstick urinalysis showed a glucose reaction of 4+, and a provisional diagnosis of epidermal atrophy of the penis secondary to type II diabetes mellitus was made.

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Topics in Primary Care Medicine

The Use of Antibiotics in Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Series' Editors

Acute bronchitis (or tracheobronchitis) is a self-limited disease with acute cough, usually productive of phlegm, and without evidence of pneumonia either clinically or by a chest x-ray film. The phlegm may be tenacious, clear, discolored, increased in amount, or foul tasting. Hemoptysis may occur. The temperature may be slightly elevated—usually not above 38.9°C (102°F)—and night sweats and fatigue are common. Shortness of breath may be worsened in patients with underlying lung disease. Occasionally there will be musculoskeletal chest wall pain, usually induced by coughing. Chest findings may include localized or diffuse crepitations and wheezes.

Laboratory tests, including sputum cultures, sputum Gram's stains, and chest roentgenograms, are not used frequently in making the diagnosis. In most instances sputum cultures (because they grow normal flora) and Gram's stains (because they show fewer than 5 leukocytes per high-powered field but no predominant organism) are not initially indicated. Chest x-ray films may be needed to help differentiate bronchitis from pneumonia. Indeed, no sign, symptom, or laboratory finding can reliably differentiate the two. An elderly patient with fever and abnormal chest findings is a case in which a chest x-ray film is useful. The absence of abnormal auscultatory findings on lung examination can exclude pneumonia with greater than 95% certainty.

Acute bronchitis may be associated with symptoms of an upper respiratory tract infection, particularly pharyngitis, although the upper respiratory tract symptoms usually fade before the cough disappears. A typical course for acute bronchitis is 7 to 14 days, although a third of patients cough for more than a month. Symptoms are more common and prolonged in cigarette smokers and in winter months.

Incidence of Acute Bronchitis

Bronchitis is a common disease. In more than 500,000 visits to general and family physicians in Virginia, acute bronchitis was the fifth most common condition diagnosed, accounting for 2.7% of all visits and 16% of visits for respiratory tract problems. In the 1980 National Ambulatory Medical Care Survey, bronchitis (unspecified) was the 7th most common condition diagnosed by general and family physicians, accounting for 1.9% of all office visits, and acute bronchitis was the 20th most common condition, accounting for another 1.1% of visits. It is estimated that in the United States acute bronchitis accounts for about 12 million physician visits a year and more than $300 million in physician visits and prescriptions. Work absences are common and probably run in the millions of days each year.

Although a diagnosis of acute bronchitis is usually made in patients without chronic lung disease, there is an association between bronchitis and asthma. Patients with a diagnosis of acute bronchitis are significantly more likely to have a previous history of asthma or atopic disease compared with controls and have a pronounced increase in subsequent visits for asthma. Indeed, the term "asthmatic bronchitis" may be appropriate to express the midrange of the spectrum that goes from acute bronchitis to asthma. In one recent study, 40% of patients with acute bronchitis but no previous history of lung disease or asthma had a forced expiratory volume in one second of less than 80% of predicted, a finding that returned to normal over a five-week period.

Chronic Bronchitis

Chronic bronchitis is defined as the production of sputum on most days for at least three months per year for more than two years. An acute exacerbation of chronic bronchitis is a clinical syndrome characterized by an increase in cough, an increased production of phlegm with altered color or tenacity, and an increased breathlessness without evidence of pneumonia—either clinically or by chest x-ray film. As with acute bronchitis, hemoptysis may occur. Wheezing is frequently present due to narrowing and obstruction in the smaller—less than 2 mm in internal diameter—airways. Most patients do not have signs or symptoms suggestive of systemic infection such as fever or leukocytosis. Increased dyspnea and chest tightness are frequently present.

(Rodnick JE, Gude JK: The use of antibiotics in acute bronchitis and acute exacerbations of chronic bronchitis. West J Med 1988 Sep; 149:347-351)

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Chronic bronchitis is generally diagnosed in association with emphysema, asthma, or both. The term "chronic obstructive pulmonary disease" reflects the overlapping disorders of chronic bronchitis, emphysema, and asthma. Whereas chronic bronchitis is defined clinically, emphysema and asthma are defined by pulmonary function tests. Sorting out these three disorders in an individual patient can be a difficult task. There is a bias to make a diagnosis in male patients of emphysema and in female patients of asthma or chronic bronchitis.

The chest x-ray film in an acute exacerbation of chronic bronchitis is normal or reflects the underlying chronic obstructive pulmonary disease. Changes may range from hyperaeration and bullae characteristic of emphysema to saccules, honeycombing, and atelectasis, which can be seen in bronchiectasis. Peribronchial cuffing is sometimes seen that represents thickening of the adventitia or mucosa around the bronchi.

Incidence of Chronic Bronchitis

Because chronic bronchitis is usually diagnosed with emphysema or asthma, the frequency with which it occurs is unclear. In one cross-sectional study of a general population, 12% of adult men and 8% of adult women had symptoms of chronic bronchitis. In the Virginia study, however, chronic bronchitis was the 114th most frequent condition diagnosed, accounting for a little less than 0.2% of all visits and 1.1% of visits for respiratory problems.

Infectious Causes of Acute Bronchitis

Table 1 lists the causes of bronchitis. For acute bronchitis, almost all causes are infectious. By far the most common is viral, accounting for well over half of the diagnoses; 180 viruses have been identified as causing upper respiratory tract infections. As a guideline, a cough will develop in 50% of patients who have such an infection, and in 50% of those a productive cough characteristic of acute bronchitis will develop. The most common viral cause of acute bronchitis is probably the rhinovirus, followed by the adenovirus. Influenza virus can cause extensive destruction of the respiratory epithelium, and respiratory syncytial virus is the usual cause of bronchiolitis in young children.

The second most common cause of bronchitis, at least in young adults, is *Mycoplasma pneumoniae.* It may account for 10% to 20% of diagnoses. The true incidence is unknown, for in the absence of clinical or radiographic signs of pneumonia, cold agglutinins are often not checked (and even if checked, may be falsely negative early in the course). Complement fixation studies are available, and a fourfold rise is indicative of a recent infection. Culturing for *Mycoplasma* is difficult, but a simplified office test is under development.

Chlamydia can also cause bronchitis. Recently a TWAR—TW for Taiwan, AR for acute respiratory disease—strain of *Chlamydia psittaci* was found to be the second most common cause of pneumonia, after *M pneumoniae,* in college students, and 5% of cases of bronchitis were associated with TWAR infection. One is faced with a problem in diagnosing TWAR infections—there is no commonly available culture technique or identification test.

A smaller portion of the cases of acute infections are due to bacteria. Sputum cultures from 80% to 95% of patients with acute bronchitis will grow out only normal flora. While it is generally accepted that normal bronchi are sterile, many bacteria, including *Haemophilus influenzae* and *Streptococcus pneumoniae,* are often found further up the upper respiratory tract, making the interpretation of a sputum culture difficult. Nevertheless, *S pneumoniae* and *H influenzae* are thought to be causes of acute bronchitis, particularly in those with more systemic symptoms.

Branhamella catarrhalis (formerly called *Neisseria catarrhalis*) is a gram-negative diplococcus recently recognized as a pathogen in acute bronchitis and in acute exacerbations of chronic bronchitis. In a recent study, it was the third most common bacterial pathogen (after *S pneumoniae* and *H influenzae*). The diagnosis is suggested from a Gram's stain where it appears as a kidney bean-shaped gram-negative diplococcus.

TABLE 1.—*Common Causes of Tracheobronchitis*

External Stimuli	Viruses
Tobacco	Influenzas A and B
Cannabis	Parainfluenzae
Air pollution	Rhinoviruses
Ammonia	Respiratory syncytial virus
Chlorine	Adenoviruses
Industrial fumes, dust	Coxsackievirus
	Coronaviruses
Bacteria	Other Infectious Agents
Haemophilus influenzae	*Mycoplasma pneumoniae*
Streptococcus pneumoniae	*Chlamydia* (TWAR)
Branhamella catarrhalis	
Bordetella pertussis	

The Cause of Acute Exacerbations

Cigarette smoking is clearly the major risk factor for the development of chronic bronchitis and emphysema. In those smoking 20 cigarettes or fewer per day (light to moderate), the frequency of chronic bronchitis is about 25%; for heavy smokers (greater than a 40- to 60-pack-year history), it increases to almost 50%. A long-term smoker who stops smoking can have a definite lessening of smaller airways obstruction as well as a reduction in coughing, sputum production, and wheezing. Other less common causes of chronic bronchitis include inhaling dust and fumes, particularly chlorine and ammonia.

The role of bacterial infections in acute exacerbations of chronic bronchitis is based more on deduction than proof. Sputum cultures are more frequently positive, but their interpretation is enigmatic. Chronic colonization of the airways with unencapsulated strains of *H influenzae* and pneumococci occurs in at least half of patients. The organisms are often found in the sputum during quiescent periods, but exacerbations are associated with a quantitative increase in the number of organisms cultured.

In summary, in acute bronchitis the cause is usually viral, with *Mycoplasma* and *Chlamydia* being less frequent and bacterial causes the least likely. In flare-ups of chronic bronchitis, environmental factors—particularly cigarette smoke—are important cofactors. The infectious causes are in a different order of frequency, with viruses still being the most common, followed by bacteria—*H influenzae, S pneumoniae,* and *B catarrhalis*—with *Mycoplasma* or *Chlamydia* being the least likely.

Treating Acute Bronchitis

The treatment of acute bronchitis is still empiric. Obviously if a patient smokes, this is an opportune time for counseling. Codeine- or dextromethorphan-containing cough suppressants may be indicated in those with significant coughing spasms or nighttime cough. Glyceryl guaiacolate, potassium iodide, mucolytic agents, antihistamines, and decongestants usually are not helpful. If influenza A is suspected, starting a regimen of amantadine hydrochloride, 100 mg twice a day—or 100 mg per day in elderly patients—within the first 48 hours will ameliorate symptoms.

The role of antibiotics in the treatment of acute bronchitis or an acute exacerbation of chronic bronchitis is controversial. Patients with a diagnosis of acute bronchitis are usually administered an antibiotic—most commonly erythromycin—even though many studies and reviews state that antibiotic therapy is not indicated. Unfortunately, most trials of the use of antibiotics for treating bronchitis were not double blind and randomized. As would be expected, numerous studies comparing the use of one antibiotic with another have shown good response to either drug.

Of five randomized controlled trials (see Table 2) of antibiotic treatment of acute bronchitis, two found no benefit from a one-week course of doxycycline, one found a reduction in symptoms and time off work when patients were treated with trimethoprim and sulfamethoxazole, one found no difference with a one-week trial of erythromycin (although there was a consistent trend favoring treatment in nonsmokers), and one found significantly fewer signs and symptoms after a ten-day course of erythromycin.

The antibiotics that might be reasonable choices for therapy are listed in Table 3, along with their antibacterial spectrum. Unfortunately, none gets all the common bacterial pathogens. The choice of whether to use an antibiotic and, if so, which one still rests with clinical judgment. At this time, our recommendation is not to treat in those who are otherwise healthy and who have no significant systemic symptoms. Acute bronchitis is a self-limited condition usually caused by viruses with a course that is not dramatically changed by giving antibiotics. In those with preexisting conditions—such as diabetes mellitus or congestive heart failure—and in those who have a productive cough along with systemic symptoms, most physicians lean towards treating for one to two weeks with one of the drugs listed—with the hope of decreasing the sputum production and perhaps preventing the occasional progression towards pneumonia or respiratory failure.

TABLE 2.—*Summary of Randomized Antibiotic Trials in Patients With Acute Bronchitis*

Study	*Definition of Acute Bronchitis*	*Subjects, No.*	*Antibiotic Used and Dose*	*Results*
Stott et al (*Br Med J* 1976; 2:556-559)	Productive cough of up to 1 wk's duration and normal findings on chest examination	207	Doxycycline, 2 initially, then 1 each d × 7 to 10 d	No difference in cough or other symptoms at 1 wk
Franks and Gleiner (*J Fam Pract* 1984; 19:185-190)	Cough productive of sputum for less than 15 d without clinical evidence of pneumonia	67	TMP-SMX, 2/d × 1 wk	At 1 wk, antibiotic group had significantly less cough, less fever, and used fewer OTC drugs; there was also a trend towards fewer days off work; smoking history did not help predict responders
Williamson (*J Fam Pract* 1984; 19:481-486)	Cough and sputum production and rhonchi or history of fever	69	Doxycycline, 1/12 hr × 3, then 1 each d × 6 d	No difference in symptoms at 1 wk or thereafter; placebo group missed less work; no difference in smokers
Brickfield et al (*J Fam Pract* 1986; 23:119-122)	Cough producing sputum for 2 wk or less and no evidence of pneumonia	50	Erythromycin, 3/d × 1 wk	Symptoms tended to resolve in nonsmokers more rapidly with treatment, with less cough and sputum production (but most not significantly different); no difference for smokers
Dunlay et al (*J Fam Pract* 1987; 25:137-141)	Acute productive cough and no evidence of pneumonia	63	Erythromycin × 10 d	Patients treated had significantly less sputum and cold symptoms, took fewer cold and cough OTC drugs, and had fewer abnormalities on lung examination at 2 wk

OTC = over-the-counter, TMP-SMX = trimethoprim-sulfamethoxazole

TABLE 3.—*Oral Antibiotics Used to Treat Bronchitis*

	Sensitivities					
Drug	*Haemophilus influenzae*	*Streptococcus pneumoniae*	*Branhamella catarrhalis*	*Mycoplasma pneumoniae*	*Chlamydia*	*Cost of 10-Day Supply, $**
Tetracycline	Equivocal	Equivocal	Yes	Yes	Yes	1.00
Penicillin	No	Yes	No	No	No	1.67
Ampicillin†	Equivocal	Yes	Equivocal	No	No	3.20
Erythromycin	No	Yes	Yes	Yes	Yes	3.38
Trimethoprim-sulfamethoxazole	Yes	Yes	Yes	No	No	2.46
Cefaclor	Yes	Yes	Yes	No	No	35.84

*Average wholesale generic price in April 1988. Retail charges to patients will be higher.

†Resistant *H influenzae* and *B catarrhalis* are susceptible to the combination of amoxicillin and clavulanate potassium (wholesale price = $39.00).

Although the appropriate length of treatment for each etiologic agent has not been investigated, 10 to 14 days of erythromycin administration would be the most logical choice for acute bronchitis, especially if one is considering a mycoplasmal or chlamydial origin. It also has good penetration into sputum. For children, erythromycin estolate has greater bioavailability and fewer side effects, but its use should be avoided in adults because of cholestatic jaundice. The most common side effects of erythromycin use are gastrointestinal. The ethylsuccinate preparation or taking erythromycin with food may decrease abdominal discomfort, although no studies have shown any one group of erythromycin to have fewer side effects in adult use.

The controlled trials do not support using doxycycline, and therefore one must also be skeptical of using tetracycline. Cefaclor and an amoxicillin-clavulanate potassium combination are expensive, and controlled trials are lacking. Trimethoprim-sulfamethoxazole is a possible choice, although it is not effective against *Mycoplasma* or *Chlamydia*. Ciprofloxacin and cefuroxime, two new oral antibiotics, have a similar spectrum for respiratory tract pathogens as do trimethoprim-sulfamethoxazole and cefaclor. Their costs are similar to cefaclor's. There are no precise guidelines for monitoring therapy—a decrease in dyspnea, less sputum, and sputum that is more mucoid than purulent are reasonable guidelines. Additional therapies to be considered in those who are not responding to antibiotic therapy include bronchodilators and inhaled steroids. Hospital admission for parenteral therapy, fluid replacement, and supplemental oxygen is rarely necessary.

Antibiotic Treatment of Acute Exacerbations of Chronic Bronchitis

There have been five double-blind controlled clinical trials of the use of common oral antibiotics (tetracycline and ampicillin) in flare-ups of chronic bronchitis. Three of these showed no significant differences in any measured variable between antibiotic and placebo use, one had a trend favoring antibiotic therapy, and one had results in antibiotic-treated patients that were significantly better than using a placebo. These studies are summarized in Table 4. The most recent study found that antibiotic treatment was 13% more successful than placebo in resolving symptoms at three weeks, although more than half of the patients with placebo treatments also had resolution. Although this difference is not dramatic, there was an additional 9% difference in the deterioration—that is, treatment failures. This resulted in increased cost and morbidity and may be the best argument for antibiotic therapy.

Clinical sense dictates that there is a continuum between bronchitis and pneumonia, and a few of those with productive cough and systemic symptoms have early pneumonia. Although it is unclear how many flare-ups are causally related to bacterial infection, it makes sense to treat with antibiotics those who appear sicker or have more severe underlying disease and therefore have a greater chance of having an early bacterial pneumonia or respiratory failure. Considering that the cost of antibiotics used to treat acute bronchitis or flare-ups of chronic bronchitis probably is in the range of $100 million each year in the US, it is noteworthy that so few randomized, controlled trials have been conducted. Based primarily on judgment, we favor treating flare-ups of chronic bronchitis with trimethoprim-sulfamethoxazole if a patient has increased sputum and dyspnea. The antibiotic is relatively inexpensive, and its bacterial spectrum matches the more common lower respiratory tract pathogens. *Mycoplasma* and *Chlamydia* are much less of a concern in older patients. Antibiotic therapy has shown the clearest success in those exacerbations with the three symptoms of increased

TABLE 4.—*Summary of Randomized Antibiotic Trials in Flare-ups of Chronic Bronchitis*

Study	*Definition*	*Patients, No.*	*Antibiotic and Dose*	*Results*
Elmes et al (*Br Med J* 1957; 2:1272-1275)	Therapy was patient-initiated at onset of acute respiratory illness; all had previously met criteria for a diagnosis of chronic bronchitis	88*	Oxytetracycline, 250 mg 4 ×/d × 5 to 7 d	No significant difference in days of respiratory symptoms; antibiotic group had trend toward fewer days off work
Berry et al (*Lancet* 1960; 1:137-139)	Worsening in the past week in those with persistent or recurrent cough with diffuse physical signs in the chest, in whom CXR has excluded other diagnoses	53*	Oxytetracycline, 250 mg 4 ×/d × 5 d	Treated patients recovered sooner if moderately severe, no difference for mild attacks (statistics not given, severity based on a 0-4 subjective score)
Elmes et al (*Br Med J* 1965; 2:904-908)	Patients admitted to hospital for acute exacerbation of chronic bronchitis	56†	Ampicillin, 1 gram q 6 hr × 3 d, then 0.5 gram q 6 hr × 4 d	No difference in hospital length of stay, change in pulmonary function test results, or sputum volume
Nicotra et al (*Ann Intern Med* 1982; 97:18-21)	Patients with chronic bronchitis who had increase in symptoms of dyspnea, cough, and sputum production without evidence of pneumonia	40†	Tetracycline, 500 mg 4×/d × 7 d	No difference in spirometry, sputum volume, blood gases, or physician or patient score
Anthonisen et al (*Ann Intern Med* 1987; 106:196-204)	COPD patients with increased dyspnea, sputum production, or sputum purulence	173*	Trimethoprim-sulfamethoxazole, 2×/d; amoxicillin, 250 mg 4×/d, or doxycycline, 100 mg/d for 2 wk	Resolution of symptoms in 21 days in 68% of those treated with an antibiotic compared with 55% with a placebo (P=.01); no significant differences between antibiotics

COPD=chronic obstructive pulmonary disease, CXR=chest x-ray film

*Ambulatory.
†Patients admitted to hospital.

dyspnea, increased sputum, and sputum purulence compared with those with only one or two of these symptoms.

The question of the prophylactic use of antibiotics in patients with chronic bronchitis is unresolved. One trial of tetracycline given over the winter months showed that prophylaxis reduced by a third time off work, but this estimate had a large range of uncertainty. Prophylaxis has no effect on the decline of pulmonary function nor on the volume or purulence of sputum. Prophylactic antibiotic therapy may be useful in those selected few who have frequent exacerbations. Trimethoprim-sulfamethoxazole or ampicillin use daily or five days a week during winter months would be a logical choice. The outpatient pharmacologic treatment of chronic obstructive pulmonary disease has recently been a topic in this series (June 1985). Ipratropium, an atropinelike aerosol bronchodilator, is a new addition to the armamentarium. Avoiding irritants such as cigarette smoking is helpful, and an acute flare-up in a patient with chronic bronchitis can provide the motivation to stop smoking—the most important therapy.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Therapeutic Endoscopy in Gastrointestinal Surgery

Rapael S. Cuhung, MD, FACS, Professor of Surgery, State University of New York, Health Science Center at Syracuse, Director, Surgical Endoscopy Service, and Attending Surgeon, State University Hospital Veterans Administration Medical Center and Crouse Irving Memorial Hospital, Syracuse, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 259 pages, $45.

Both the strengths and the shortcomings of this book are due to its single authorship. There are the uniformity of opinion, lack of redundancy, and good organization that go along with a single author. The writing style is excellent throughout. There is a uniform use of pertinent illustrations rather than a plethora of radiographs and endoscopic photographs that are meaningful only to the author. The recent advances in therapeutic gastrointestinal endoscopy are discussed in a most thoughtful and comprehensive manner. The organization of each of the sections lays out a brief but thorough discussion of the pathologic anatomy and pathophysiology, followed by the indications and contraindications for the procedure and a comparison with alternative operative management. The sections on results and complications of these techniques are quite good. Unconfusing algorithms of management summarize the textual material and reflect a consensus of thought of most experts in the field.

The shortcomings of the book are also due to its sole authorship. In the sections on equipment, technique, and postprocedural management, the author's bias is strongly expressed and does not necessarily represent the standard of care in endoscopy units in this country. The writer's opinions are sometimes expounded as "the truth" and alternative points of view are not explained.

In comparison with the many atlases of therapeutic endoscopy that have appeared on the market in the past two years, this work has significant value. It expresses a surgical opinion for the first time against a tide of medical opinions on therapeutic endoscopy, and this opinion is expressed concisely and with a great deal of intelligence. All told, this is an excellent, well-written, comprehensive presentation of a thoughtful surgical endoscopist's approach to therapeutic endoscopy. It is a best buy at $45 and belongs in the libraries of all physicians interested in this field.

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Seminars in Health Care Delivery

Building a Consensus for Physician Payment Reform in Medicare

The Physician Payment Review Commission

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This feature appears regularly in THE WESTERN JOURNAL OF MEDICINE. *It is intended to cover recent developments in a broad range of issues that will have an impact—either directly or indirectly—on clinical practice. Occasionally the seminars may include informed speculation about likely future developments.*

STEVEN A. SCHROEDER, MD
Series' Editor

In recent years physician payment under Medicare has risen to the top of the federal health policy agenda. For more than a decade before 1984, the focus had been on containing hospital costs. The current concern of federal policymakers about the rapid increase in Medicare Part B expenditures and diminishing beneficiary financial protection has its origins in the original Medicare legislation.

In 1965, when the legislation creating the Medicare program was enacted, limited time was available to settle on a method of paying physicians. A system of payment of "customary, prevailing, and reasonable" charges, which was beginning to come into use in Blue Shield plans, was chosen. Despite widespread dissatisfaction, the system remained essentially unchanged for almost 20 years.

After the enactment of legislation in 1982 and 1983 that affected hospital payments in the Medicare program, in 1984 Congress turned its attention to physician payment. Pressure to reduce outlays of monies for Medicare had led to the development of the "prospective payment system" for payments to hospitals, and Congress decided to look at physician payment to meet budget reduction targets. In that year, Congress froze payments to physicians and created the participating physician program, which offers incentives to physicians who agree to accept the Medicare-allowed charge as payment in full on all services. In the following year, the freeze was extended to achieve additional budget savings.

At that point, Congress decided that more fundamental reform in Medicare physician payment was needed and created the Physician Payment Review Commission (PPRC) to work with it to chart the course of reform. The PPRC began operation in late 1986.

Congress modeled the PPRC on a commission that it had created in 1983 to deal with hospital payment—the Prospective Payment Assessment Commission[1]—but gave it a very different mandate. Whereas that commission was charged with advising the Secretary of the Department of Health and Human Services on implementation of the prospective payment system, the mandate of the Physician Payment Review Commission emphasizes advising the Congress on basic reform needed in physician payment. The PPRC was created to help develop reforms rather than to advise on implementing a program that had already been enacted.

The PPRC has 13 members appointed by the Office of Technology Assessment, a congressional support agency. Six of the current members are physicians and three are economists. The others have backgrounds in nursing, insurance, consumer organizations, and employee benefits.

Medicare and Physicians' Services

When the Medicare program was established in 1965, Congress adopted policies for physician payment that were designed to gain the support of the medical profession for the program. The law instructed insurers—called carriers—who administered the Part B program to consider the following criteria when determining physicians' charges that would be allowed by Medicare:

> . . . [A]ssure that, where payment . . . is on a charge basis, such charges will be reasonable and not higher than the charge applicable for a comparable service and under comparable circumstances to the policy holders and subscribers of the carrier. . . . In determining the reasonable charge . . . [t]here shall be taken into consideration the physician's customary charge for similar services . . . as well as the prevailing charges in the locality for similar services.[2]

Congress had adopted a system for paying physicians that had been used for little more than a decade in a few Blue Shield plans (Wisconsin; Iowa; Riverside County, California), largely on an experimental basis. The Medicare program described this as the "customary, prevailing, and reasonable" system of payment. This system was more commonly known as the "usual, customary, and reasonable"

(Lee PR, Ginsburg PB: Building a consensus for physician payment reform in Medicare—The Physician Payment Review Commission. West J Med 1988 Sep; 149:352-358)

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ABBREVIATIONS USED IN TEXT

DRGs = diagnosis-related groups
PPRC = Physician Payment Review Commission

system.[3] Both of these systems are based on charges by individual physicians, charges by physicians in the same geographic area, and the concept of reasonableness (Table 1).

Physicians are paid on the basis of "customary, prevailing, and reasonable" charges. A physician's actual charge is subject to two screens. The "customary" screen reflects what the physician charged for the particular procedure during the previous year. The "prevailing" screen is set at the 75th percentile of customary charges of other physicians by specialty and geographic area during the previous year. In California, for example, the Medicare Part B program establishes separate fee screens for more than 30 specialties in each of 28 geographic areas designated within the state.[3] Since the mid-1970s, increases in prevailing charge screens have been limited to increases in the Medicare Economic Index, which measures increases in physicians' costs of practice.[4]

Physicians can choose whether to bill the Medicare program directly or to bill their patients, who in turn will bill the program. If a physician bills the program, he or she must agree to accept the Medicare-approved charge as payment in full—that is, bill the beneficiary only for the applicable deductible and coinsurance amounts. This is called accepting assignment. Those physicians not accepting assignment are permitted to bill their patients for a higher charge than the Medicare program allows.

Medicare Reform and Physician Payment, 1984-Present

In 1984 Congress began a series of actions that has changed physician payment by Medicare's Supplementary Medical Insurance program in notable ways. Particularly important have been the Deficit Reduction Act of 1984, the Consolidated Omnibus Budget Reconciliation Act of 1985, the Sixth Omnibus Budget Reconciliation Act of 1986, and the Omnibus Budget Reconciliation Act of 1987.

The issues that Congress began to address in 1984 included the following:

- Physician assignment and beneficiary liability;
- The rapid and continuing increase in supplementary medical insurance expenditures;
- The incentives in the customary, prevailing, and reasonable system of payment for physicians to inflate their charges to receive higher payments in subsequent years;
- Perceived inequities in fees between medical and surgical specialties, between generalists and subspecialists, and between technical or invasive procedures and services that involve management, diagnosis, and counseling[5];
- Fee rigidity in the face of advances that reduce the cost of providing services[6];
- Inequities between payments to physicians in urban (high) and rural (low) areas[7];
- The incentives of the customary, prevailing, and reasonable (and other fee-for-service) systems of payment to result in the higher volume of service that is necessary for appropriate care[8]; and
- Incentives to increase the volume of laboratory services.

Of particular concern to Congress was the rapid increase in Medicare's Part B expenditures, which are now more than five times greater than just ten years ago.[9] In 1987, Part B spending totaled $31.6 billion; by 1988 the figure was $36.4 billion. These expenditure increases reflect not just general inflation but real spending per Medicare enrollee, reflecting both a greater volume of service and an increased complexity of services provided. From 1970 to 1975 the annual rate of increase of Part B expenditures was 13.7%, increasing to 20.8% from 1975 to 1980 and 16.2% from 1980 to 1985. More important, real spending per enrollee increased 9% in 1975 to 1980 and 8% annually from 1980 to 1985 (Table 2 and Table 3).

Within the overall growth of payments for physicians' services, some striking patterns have emerged. There is a noticeable trend towards increasing expenditures for the services of specialists, particularly those who use considerable equipment when providing care. Three categories showing the highest growth rates between 1975 and 1982—ophthalmology (26%), radiology (23.6%), and cardiovascular disease (17.8%)—are all technically intensive specialties.[10] Low-growth specialties were family and general practice, general surgery, and urology, followed closely by internal medicine.

In those specialties with a high rate of increase, the most striking finding was the increase in volume of services per enrollee. While services per enrollee between 1975 and 1982 declined 1.3% for general surgery and did not change for general and family practice, they increased 7.6% for specialists in ophthalmology, 10.5% for radiology, and 10.8% for cardiovascular disease. From 1975 to 1982,

TABLE 1.—*Terminology Used By Third Parties for UCR (Profile) Methods of Reimbursements**

	Fee Screen Levels		
	Level I	*Level II*	*Level III*
Third party	Individual physician	Geographic area	Reasonableness
Medicare (Part B)	Customary	Prevailing	Reasonable
AMA definition	Usual	Customary	Reasonable

AMA=American Medical Association, UCR=usual, customary, reasonable

*Adapted with permission from Showstack et al.[3]

TABLE 2.—*Medicare Supplementary Medical Insurance Part B Payments**

	Fiscal Years			
Amount	*1970*	*1975*	*1980*	*1985*
Total (billion $)	2.2	4.2	10.7	22.7
Per enrollee ($)	112.0	174.0	396.0	762.0

*Adapted with permission from Etheredge.[9]

TABLE 3.—*Growth in Medicare Supplementary Medical Insurance Part B Payments**

Annual Growth Rate	*1970-1975, %*	*1975-1980, %*	*1980-1985, %*
Total	13.7	20.8	16.2
Per enrollee	9.2	17.9	14.0
Consumer Price Index	6.7	8.9	5.2
Real spending per enrollee	2.5	9.0	8.0

*Adapted with permission from Etheredge.[9]

Medicare spending increases for general surgeons were largely the result of price increases (15% per year) rather than volume increases.[11] Congress also found notable geographic variation in payments to physicians for similar services, as well as differences among specialists for what appeared to be similar services.

Another area of concern to policymakers and beneficiaries has been the rapid increase in out-of-pocket expenditures incurred by the elderly. Beneficiaries' out-of-pocket liability for acute care services comes from expenditures for Part B premiums, private supplemental health insurance premiums, coinsurance and deductibles for Parts A and B, extra billing by physicians above the charges approved by Medicare, and charges for services not covered, such as prescription drugs. Costs per beneficiary can vary substantially, depending on whether patients have been in hospital, whether they have substantial prescription drug or other non-covered services outside the hospital, and whether their physicians accept assignment. Average out-of-pocket costs per beneficiary for Part A and Part B were about $1,000 in 1985.

To address issues related to physicians' frequent unwillingness to accept assignment and the potential this posed for beneficiary liability, Congress created a new category of participating physicians in the Deficit Reduction Act of 1984. Those physicians who agree to accept assignment for all Medicare services for a year are participating physicians. They are listed in directories that are widely distributed, and they have prevailing fee screens that are 4% higher than those for nonparticipating physicians.

In 1984 Medicare began limiting the amounts that physicians could charge beneficiaries. In that year customary and prevailing fees for all physicians' services were frozen; charges for the 70% of physicians who refused to accept assignment were also frozen.[12] The 1986 Consolidated Omnibus Budget Reconciliation Act lifted the freeze with a 4% increase in prevailing fees for participating physicians.

In January 1987 the Sixth Omnibus Budget Reconciliation Act lifted the freeze for all physicians and fixed the increase in prevailing fees at 3.2%, while maintaining the difference between participating and nonparticipating physicians. Nonparticipating physicians, however, were subjected to maximum allowable actual charge limits for four years. In a complex formula, these limits allow physicians with relatively low charges to raise fees more than those with high charges.

The Deficit Reduction Act of 1984 also prohibited physicians from billing for services not provided in their offices. Physician payment was limited to a maximum $3 fee for tests sent to outside laboratories. Areawide fee schedules for laboratory tests were also instituted, whether done in a physician's office or by an independent laboratory. Subsequently, the Consolidated Omnibus Budget Reconciliation Act placed ceilings on regional fee schedules.[11]

Against this background of rapidly rising costs and issues related to customary, prevailing, and reasonable fees and physician assignments, Congress in 1985 created the Physician Payment Review Commission and provided funding in October 1986. The commission was to provide advice to Congress and the Department of Health and Human Services on reforms in the methods used to pay physicians for services to Medicare beneficiaries. This commission began its work in November 1986; it issued its first report in March 1987 and its second report in March 1988.

Physician Payment Review Commission

The commission's first report[13] discussed

- The commission's roles and mandate;
- The criticisms of Medicare's current method of paying physicians that led to the creation of the commission;
- The goals that have guided the commission's recommendations and the tradeoffs among goals that the commission and the Congress must face; and
- The major recommendations of the commission and its next steps.

Roles and Mandate

The commission has defined four broad roles for itself. First, it serves as a source of independent expert advice to the Congress and to the Secretary of Health and Human Services. Second, it provides opportunities for beneficiaries, physicians, and other interested parties to have their views considered in policy deliberations on physician payment issues. Third, the commission conducts objective analyses to provide a basis for policy decisions to alter Medicare's method of paying physicians. Fourth, it does some of the design work necessary to implement major changes in physician payment.

The Congress called for PPRC to submit its recommendations by March 1 of each year. The legislation directs the commission's attention to the methods of adjusting reasonable charge levels, setting rates, and making payment for physicians' services. The mandate also requires that more specific issues be considered, including differences in payments based on specialty or geographic location, the use of assistants at operative procedures, and acceptance of assignment by physicians.

Current Payment Method

The "customary, prevailing, and reasonable" method of payment has come under increasing criticism because of the poor incentives for providing cost-effective services. In particular, it has been criticized for encouraging increases in physicians' charges and service volume; creating patterns of allowed charges that embody inappropriate incentives for the use of medical services and for physicians' decisions on where to locate and how to specialize; and being administratively complex and difficult for both physicians and beneficiaries to understand.

Physician Payment Policy Goals

The Medicare program was designed to provide the elderly with financial protection from the costs of medical care and, in the process, to increase access to services of high quality. In assessing options for reform in physician payment, the commission is guided by several goals.

Access to care. Reforms in the methods of paying for physicians' services must ensure that all beneficiaries have access to medical care. For those beneficiaries electing to continue to receive care through the fee-for-service system, free choice of a physician must be maintained.

Quality of care. Reforms should maintain or improve the quality of care provided to Medicare beneficiaries. Beneficiaries should receive high-quality care provided through efficient medical practice.

Financial protection for beneficiaries. Changes in the payment to physicians should maintain financial protection

for beneficiaries. While it may be appropriate for patients to have some financial responsibility for the cost of care, levels of responsibility should not be so high that they prevent beneficiaries from gaining access to care or impose significant economic hardship. The commission is particularly concerned with limiting the responsibility of beneficiaries for charges in excess of what Medicare allows. It is also concerned that the growing shift of care to outpatient settings, which brings many noneconomic benefits to patients, should not subject beneficiaries to undue financial burdens because of the less generous coverage and payments provided for most out-of-hospital services.

Equity among physicians. Reforms in the levels or methods of payment should increase equity among physicians so that similar payments are made for similar services among similarly qualified physicians. Differences in payments for different services should broadly reflect relative costs, market conditions, and other appropriate factors.

Reduction in the growth of supplemental medical insurance outlays. Changes in physician payment should slow the growth in federal outlays for supplementary medical insurance. The growing burden on taxpayers, who underwrite 75% of program costs through general revenues, and beneficiaries, who underwrite 25% of the cost through premiums, is becoming an increasingly serious problem. One way to reduce costs rather than merely shift them to others is to encourage increased efficiency in the practice of medicine. This can be achieved through more appropriate payment incentives to physicians, utilization review, research, and education. In evaluating policy changes that reduce outlays in Part B of Medicare, the potential for offsetting increases in outlays for Part A of Medicare must be considered.

Understandability. Reforms should make the method of paying physicians easier for beneficiaries, physicians, and the general public to understand. Physicians should know what charges Medicare will allow, and, in turn, beneficiaries should be informed by physicians of what they are expected to pay. When feasible, this information should be provided before a service is rendered.

Orderly change. Changes in the method of payment should be orderly and coherent. Short-term changes should be consistent with long-term policy goals. The feasibility of administering specific changes must be taken into account, especially in setting schedules for their implementation. As major reforms are implemented, monitoring of their effects should be given high priority because these effects are uncertain and mid-course corrections may be required.

Pluralism. Reforms in payment methods should accommodate the various ways health services are organized. Both fee-for-service methods and capitation should play roles in the provision of medical care in the United States.

One central challenge to policy is to find a way to incorporate society's concerns about limited resources into physicians' decision making while maintaining the physician's freedom and responsibility to exercise clinical judgment on behalf of the patient.

Recommendations and Plan

The commission has considered four general alternatives for reforming the way physicians are paid under the Medicare program: refining the current payment system, making payments according to a fee schedule, creating a system of all-inclusive fees for defined packages of services, and increasing the use of capitation payments. In its initial report, the commission focused on the first two alternatives. The others, which present more problems and questions for near-term adoption, will be taken up in subsequent reports.

The commission has charted a course to follow for the long term and has recommended immediate improvements in the current payment system that are consistent with long-term objectives. The first recommendation describes plans to develop a fee schedule. Other recommendations apply primarily to the current payment system, but they also will be relevant to the adoption of a fee schedule.

Recommendations

A Fee Schedule

The commission endorsed the concept of a fee schedule for Medicare in its first report. Under such an arrangement, the pattern of payments for services would differ from that under the current system by type of procedure, practice setting, geographic location, and perhaps by specialty. Adoption of a fee schedule requires major decisions in design. For example, how should relative values be determined? How are payments to vary by practice setting and geographic location? How should the payments be updated over time? Is a different policy concerning assignment needed?

In its second report, issued March 31, 1988,[14] the commission recommended basing a relative value scale for Medicare physician payment primarily on the resource costs of providing services. These costs include physicians' own time and effort and their costs of practice: rent, staff salaries, and malpractice insurance premiums, for example. The only practical near-term alternative to a scale based on resource costs is one based on physician charges. Such a scale would largely incorporate the distorted incentives that created the demand for payment reform in the first place.

A relative value scale based on resource costs would promote a more appropriate and efficient allocation of medical services and should generally be seen by physicians as more equitable. Today, a physician can make several times more per hour doing endoscopies than evaluating patient problems and developing treatment programs. Payments for procedural services such as pacemaker insertion and cataract operations that are excessive in relation to their resource costs may lead to overuse of these services. The financial promises made in advertisements for much diagnostic testing equipment suggest that these services may be overpriced, as well. The results of overpricing are increased outlays without comparable improvements in care.

Designing a sound, comprehensive relative value scale based on resource costs presents several technical problems. Many of these problems and some possible solutions are illuminated in a congressionally mandated project being undertaken at Harvard University by Dr William Hsiao and his colleagues. Dr Hsiao will report on research to design a relative value scale for services and procedures in 18 specialties. The commission will analyze carefully the project's assumptions and methods, simulate its effects on physicians and beneficiaries, and conduct public hearings to solicit the reactions of medical, consumer, and other interested groups. It will also examine related research and consider the approaches taken by other payers in this country and elsewhere. If the commission finds inadequacies in the work done to date, it may sponsor further surveys and convene consensus panels to propose refinements.

Geographic Variation

In addition to setting relative payments for different types of physician services, a fee schedule must specify how payments will vary by geographic area. The commission's analyses indicate that geographic variation, although not trivial, is less extreme than generally believed. Differences in physician costs of practice, although important, explain less of this variation than might be expected. Following the commission's principle that payment levels should be tied to resource costs, a cost-of-practice index to guide geographic adjustments in fees is being developed. We are also searching for factors that may not be adequately captured by such an index: the special circumstances of rural areas, for example.

Inherent Reasonableness and Overvalued Procedures

While the commission endorsed the use of recently enacted provisions on inherent reasonableness to make interim changes in relative payments, it developed a simpler approach to identify procedures overvalued by Medicare. Medicare relative values for selected services were analyzed and compared with values developed by other payers through negotiation, assessment of resource cost, or other non-change-based methods. As a result of this analysis, the commission identified 13 overvalued procedures (coronary artery bypass graft operations and total hip replacement, for example) that Congress used in reducing Medicare payments.

Assignment and the Participating Physician Program

Congress has done much to encourage physicians to accept Medicare-allowed charges as payment in full. Physicians currently accept assignment for nearly 75% of Medicare claims. Still, beneficiaries paid over $2.5 billion in 1987 for balance billing on nonassigned claims. The commission is sensitive to beneficiary liability for extra billing but is also aware of the importance to physicians of Medicare's traditional policy that lets physicians choose whether or not to accept assignment.

The commission has not yet made recommendations on assignment, but our March report has developed much of the background for future decision making. The major dimensions of policy on assignment are,

- Should policy cover all services and beneficiaries or focus selectively?
- Should extra billing be eliminated or, as now, limited in some way?
- What relative balance should be sought between policies to encourage assignment versus policies to prohibit or limit balance billing?

Medicare Economic Index

For more than a decade the Medicare Economic Index has limited rates of increase in allowable charges. While the rates have been updated periodically, the index continues to be applied to 1973 prevailing charges. The commission plans to examine a number of methods for updating the base of the index so that the relative prevailing charges of 15 years ago do not play so large a role. The updating is likely to have a substantial effect on relative payments, so before recommending a specific method, the commission wants to ensure that changes are generally consistent with the types of fee schedules contemplated and that those changes would not increase program expenditures.

As an initial step, the commission recommended a reduction in the annual update of prevailing charges for all services except primary care, which the commission identified as office visits, nursing home visits, and home visits. When Congress adopted the commission's recommendations, it added emergency room visits.

Program Administration

Improvements in program administration are a key element in Medicare physician-payment reform. Recommendations cover four areas: funding, flexibility for carriers, standards for carriers, and research on effective carrier activities.

Adequate funding of Medicare administration is necessary to protect beneficiaries and contain benefit costs. Funding levels should reflect the complexity and scope of program requirements. The funding provided to carriers can go further if carriers are given greater flexibility to allocate funds to their most productive uses.

At the same time, strong standards for carriers' processing of claims in areas such as prompt payment, accuracy, and service to beneficiaries and physicians should be a priority, and persistently poor performers should be replaced. With respect to prompt payment, the PPRC is concerned that President Reagan's fiscal year 1988 budget requests forecast an increase in the average time for processing claims from 15 days in 1986 to 20 days in 1987 and 26 days in 1988.

The effectiveness of various carrier activities has not been adequately studied. The commission recommends that the Health Care Financing Administration expand research to identify cost-effective utilization review and other benefit cost management techniques used by carriers, professional review organizations, and private payers.

Coding

Lack of refinement and standardization in coding of procedures has been a serious problem in administering physician payments and could be a limiting factor in implementing a fee schedule. The definition of codes for medical and surgical services, including those representing services covered by global fees for surgery, should be refined and standardized. The commission will convene an interspecialty consensus panel to develop a generic description of surgical global services. Physician experts will then identify the components of specific surgical procedures. In order to understand more fully the problem of coding for visit services, the commission will survey physicians to determine how they interpret the differences in current codes.

Specialty Differentials

The commission has started to define a uniform national policy for specialty differentials. Again, the basic principle is that payment differences should reflect differences in resource costs rather than differences in specialty designation. Many services are provided only by one or a few types of specialists, and resource-based payments for those procedures and service codes should capture the value of specialists' work. Office and other visits are an exception to this pattern and may need to be paid differently for different specialists or coded differently to better reflect systematic variations in the content of visits.

Assistance at Surgery

Medicare typically pays for assistance at surgical procedures by physicians and others. Serious doubts have been raised about how frequently physicians are needed as assis-

tants and whether payment by Medicare is appropriate. Medicare limits on payment for assistance at surgical procedures should be supplemented by additional definitions and guidelines. An assistant should be defined as a person who has the necessary qualifications to participate in the particular type of operation and who actively assists a surgeon in a surgical procedure. Medicare also must specify practical guidelines for claims review by carriers. The commission plans to test the use of panels of surgeons and others to develop practical guidelines for carriers.

Diagnosis-Related Groups

The commission also took up the issue of whether Medicare should pay radiologists, anesthesiologists, and pathologists on the basis of diagnosis-related groups (DRGs). After studying the issue and hearing extensive testimony, the commission decided not to endorse DRGs for these specialists. There are problems with current methods of paying hospital-based physicians, but DRG payment is not the best way to address them. The commission plans to examine alternatives within fee-for-service payment.

Data

Timely, relevant, and accurate data are crucial to the consideration of reforms in Medicare physician payment methods, and to program management, quality assessment, and utilization review. The commission notes the recent progress in improving data systems by the Health Care Financing Administration and encourages continued efforts in this area, particularly those mandated by the Congress in recent legislation. The commission will assist the Health Care Financing Administration and other federal agencies in their planning of future improvements in Medicare data.

Utilization of Services

Although a fee schedule is likely to encourage more appropriate choices among diagnostic and treatment options, it generally retains the incentives for overuse that plague fee-for-service payment methods. The commission is considering both shorter- and longer-term strategies to deal with the volume problem. On both fronts, strategies should selectively reduce services of least benefit without threatening the many valuable services for which Medicare pays.

Success in controlling volume will require the following:

- Medicare beneficiaries and their physicians must be willing to forego services of little or no benefit.
- All parties—physicians, beneficiaries, and others who influence medical choices—must have more usable and complete information about the effectiveness of alternative medical services.
- There must be incentives to use such information to eliminate unnecessary or minimally beneficial care.

Utilization review. The commission thinks that utilization review in Medicare can become more effective in controlling volume and more credible within the physician community. This will require more systematic evaluation of the clinical soundness of existing review efforts, more careful assessment of the impact of different methods for review, and more research to focus program efforts and physician responses on real utilization problems. Several private organizations are doing sophisticated work to increase the efficiency and quality of utilization management. Medicare policymakers should consider how it might use this work—either directly or as a guide to innovation and refinement in professional review organization and carrier review activities.

Practice guidelines and feedback. Because utilization review is a relatively costly, intrusive, and limited tool, additional strategies are needed to improve physician knowledge and application of effective and efficient styles of practice. The commission is particularly interested in two approaches: practice guidelines for specific services and feedback to physicians of information on how their practice patterns compare to others'.

Our knowledge of what treatments work for what patients is incomplete, and much more controlled clinical research on the outcomes of new and existing treatments is needed. Even so, the knowledge we already have could be better used by physicians and patients. Both feedback and practice guidelines can help bring scientific knowledge more fully to bear on the day-to-day practice of medicine. The commission will be soliciting the advice of the medical community and others on what the priorities, funding, processes, and structure of a strategy for such knowledge development and transfer should be.

Expenditure targets. The commission is also investigating a more global approach to the volume problem, that is, expenditure targets. The idea would be to adjust updates in physician fees up or down on the basis of how total expenditures match a predetermined target. If physicians could collectively control the volume of services, they could achieve a full scheduled increase in fees (or more) and free themselves from some intrusive regulation. Key questions about this kind of approach are how would individual physicians respond and how could the medical community support and encourage a constructive response. The feasibility of such an approach also depends on a variety of technical and policy factors, including the quality and timeliness of expenditure data, the variables to use in projecting trends and setting targets, the effectiveness of quality assurance techniques, and the mechanisms for tying global targets to payment administration. These issues are on the commission's agenda for the coming year.

Conclusions

The commission thinks that the steps outlined in its 1988 report to Congress, many of which have been summarized here, can help control the rate of increase in Medicare outlays for physician services. We must stress, however, that quick and simple solutions to the problem of rising costs do not exist. Notable progress will require that a variety of responses be developed and pursued over a sustained period.

Without underrating the potential for positive change, we must be sensitive to the important limitations on what Medicare payment policy can accomplish. For example, Medicare generally is not as big a factor in physician income as it is in hospital income, although some specialties do depend heavily on revenues from the program. This may limit the magnitude of change that Medicare can achieve, particularly if private payers—insurers and large private employers—do not alter their payment schedules.

Other factors are outside the reach of payment methodology altogether. For one, continued increases in the supply of physicians will be a powerful force towards additional services, even if greater competition depresses fees. And the success of direct attempts to control the volume of services will depend, in part, on the attitude of the general public

towards foregoing medical procedures of uncertain benefit. In addition, fears of malpractice suits may dampen physician interest in economizing on the use of services. For these reasons and more, a comprehensive approach to containing costs must go beyond reform in the way Medicare pays physicians.

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Health Care Delivery

Uncompensated and Undercompensated Care Provided by San Francisco Medical Society Physicians

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Practicing physician members of the San Francisco Medical Society were surveyed regarding reimbursement rates for medical care provided to underinsured and uninsured patients. Of 394 respondents, about $51,000 per physician practice was written off as uncompensated care or services not billed for in 1985. An average of 7% of each physician's patients was estimated to be "no-pay" or charity patients, accounting for $19,000 of this total. Almost $32,000 was reported as being uncompensated care, or that which is billed but not paid. In addition to these amounts, an average of $32,000 was reported as being discounted from the usual fee levels by government insurance programs. Extrapolating these results to the physician membership of the local medical society indicates that physicians in San Francisco may be providing as much as $81 million in uncompensated or charity care annually. These results emphasize that private practitioners are providing a significant amount of medical care at reduced or charity rates, an amount that can be expected to increase given present trends. Substantial changes are needed if the burden of providing medical care to poor and uninsured Americans is not to fall disproportionately on private providers.

(Hogeland S: Uncompensated and undercompensated care provided by San Francisco Medical Society physicians. West J Med 1988 Sep; 149:359-361)

The problem in the United States of funding medical care for medically indigent persons—those without personal funds or health insurance—continues to become more serious. As the costs associated with health care rise and government funds for providing care and health insurance become scarcer, increasing numbers of Americans are left without easy access to medical care. At all levels, government officials are cutting programs. The burden of providing care at reduced or nonexistent reimbursement rates is falling increasingly on the private sector. This study represents an attempt to assess the impact of these trends on practicing physicians in San Francisco.

Medical Care Reimbursement Environment

Until 1982, health care for medically indigent adults—those who do not qualify for Medi-Cal (Medicaid) on a regular basis—was nonetheless covered by the state of California through its Medi-Cal program. At that time, Medi-Cal "reform" legislation was enacted, and the responsibility for providing for these persons was turned over to the individual counties.[1] That year, the state paid as much as 70¢ on the dollar of former funding levels. The cost of administering the program also became county responsibility, but no funds were provided for this purpose by the state. By 1987, the state paid only 55¢ on the dollar. San Francisco County general revenues were required to make up the difference.

The crisis faced in San Francisco is further exacerbated by the fact that Medi-Cal reimbursement to physicians is estimated to be only 41% of usual fees, down from 50% before Medi-Cal "reform" (J.S. Taub, "Medi-Cal: An Ailing Health System for the Poor," *California Journal*, 1987; 43:432). Like other major urban areas, San Francisco is particularly hard hit by reductions in public funding of health care. The county government's contribution to indigent care—for the homeless, patients with the acquired immunodeficiency syndrome, employed but underinsured or uninsured patients in catastrophic situations—reached $100 million in 1985 (Margaret Kisliuk, Executive Assistant, Office of the Director of Health Services, San Francisco County Department of Public Health, oral communication, October 1987).

The San Francisco Medical Society (SFMS) surveyed its members to assess the sources and amount of payments for medical care provided to patients. The survey was undertaken to assist a local coalition, the Bay Area Health Task Force, to improve access to needed health care services for San Francisco's underinsured and uninsured citizens and to assess the financial impact on providers serving that patient population.

The data would be provided to the task force—a coalition of business, labor, government, and providers in which the medical society is a participant—for use in examining access problems and the financial jeopardy faced by providers rendering care at no or reduced charge for indigent patients. Such data on hospitals are readily available through the California Health Facilities Commission, but similar data on physicians have not previously been available.

To help define the magnitude of the problem, the SFMS agreed to fund a survey of its members. To avoid conflict-of-interest charges, we worked cooperatively with the Bay Area

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ABBREVIATIONS USED IN TEXT
BAHRC = Bay Area Health Resources Center
SFMS = San Francisco Medical Society

Health Resources Center (BAHRC), a reincarnated Health Systems Agency. BAHRC was a member of the task force with survey expertise and computer tabulation analysis capabilities.

Methods

After two pretests, 1,739 questionnaires were mailed from the SFMS on November 19, 1986, with an explanatory letter and a request that they be returned by December 1, 1986. Financial limitations prevented follow-up by mail or telephone. A decision to exclude hospital-based physicians—radiologists, anesthesiologists, and pathologists—reduced the sample to 1,600. With 2,200 active and retired members (retired members were excluded from the survey), the SFMS membership represents about 60% to 65% of all physicians licensed to practice medicine in San Francisco County and a higher percentage of those practicing in private, noninstitutional settings.

The questionnaires were tabulated in January 1987. After adjusting for the excluded specialists, 394 were returned for a valid response rate of 25%, which is high for a mail-in survey without follow-up. BAHRC warns there may be possible bias by a selective return. Physicians responding may have been those most affected by the uncompensated care issue. Budgetary constraints also prevented follow-up to determine why the remaining 75% of members did not respond to the survey.

The survey was designed to measure the opinions of local physicians regarding the amounts of medical care provided to the underinsured and uninsured of San Francisco. To maximize physicians' responses to the survey, the surveyors sought estimates rather than a more precise accounting of service provided. The results represent physicians' perceptions of the amounts of care they provide to the underinsured and uninsured. The survey sought information only from members of the SFMS. Nonmembers were not surveyed, which could further affect results.

Results

The respondents' profiles closely correspond with those of the SFMS membership when compared by specialty, age, and geographic location (zip codes) of their practices. SFMS physicians estimate that an average of 19% of patients in their practices are uninsured by any source. Among respondents, about $51,000 per physician practice, exclusive of discounted services for Medicare and Medi-Cal, was written off for uncompensated care or services provided but not billed for in 1985. For respondents alone, this is equivalent to $13,770,000. Extrapolated to the survey universe—that is, the remaining 75% of nonresponders—the amount of uncompensated and charity care would equal $81.6 million annually.

Respondents estimated they had a cumulative total of 863,000 outpatient visits in 1985—which extrapolates to 4,469,000 patient visits annually for the survey universe—2,793 outpatients per physician based on a 49-working-weeks year, or 57 patients per week. In all, 7% of patients are estimated to be charity care ("no pay") patients. Therefore, as many as 313,000 charity care visits may be provided by the SFMS survey universe members annually. An estimated $215,828 in gross charges would be billed annually by the average medical practice in San Francisco if all charges were billed. Respondents reported, however, that $19,000 is never billed but represents charity care. A total of $31,600 is written off as uncompensated care—given at a reduced cost or billed for with no expectation of payment, as opposed to bad debt; another $32,600 is discounted from usual charges by the Medicare and Medi-Cal programs.

A projected 70% of SFMS members are providing free or reduced-cost care to patients who lost their health insurance coverage in 1986. Another 55% could be projected to be providing free or reduced-cost care to patients who lost their Medi-Cal coverage. On average, respondents reported discounting the cost of care provided to lower income, uninsured patients by 42%. Free or discounted care to lower income, uninsured patients is provided by a large majority of SFMS members in both the inpatient (60% of physicians) and outpatient (61% of physicians) settings. An average of 50% of charges to uninsured low-income patients was collected. One in four survey respondents reported 10% or more of the care they provided went to charity care patients for whom no payment at all was received.

In general, SFMS members report that they do not require their uninsured patients to establish a payment plan (56%), and 76% do not require a downpayment or full payment at the time of service.

Of the patients treated by the typical survey respondent, 54% are on government insurance programs including Medi-Cal, Medicare, and Civilian Health and Medical Programs of the Uniformed Services (CHAMPUS). This figure appears somewhat high and could reflect a selective response by physicians who treat higher numbers of the underinsured and uninsured. Respondents report that they are reimbursed for only 64% of claims submitted to the Medi-Cal program. In addition, 90% say Medi-Cal payments are too low, 66% say payment is too slow, and 71% say the program's paperwork is too burdensome. Still, 85% indicate they participate in the Medi-Cal program, though the survey did not ask what percentage of their total patient loads were Medi-Cal beneficiaries. The California State Department of Health Services data for 1986-1987 indicate that in San Francisco County, 1,762 solo practitioners and 234 groups (of unknown numbers of physicians) received payments from the Medi-Cal program (John Keith, Department of Health Services, Chief of Medi-Cal Statistics, oral communication, January 1988). Past SFMS analyses of members have indicated that nearly 90% accept some Medi-Cal patients, although this is clearly an area for additional analysis.

Physicians responding to the survey appear to be aware of their patients' financial situations (respondents say 60% of their uninsured patients are lower income or poor), and they say they are responsive to those financial situations within their practices.

Comments

Self-selection among survey respondents is an acknowledged possibility, but the sample is generally representative of the SFMS membership (excluding hospital-based physicians). In fact, figures reported by physicians relative to the percentage of patients without health insurance within their practices is lower than, but still consistent with, findings

from a study done by the Stanford Research Institute for the Bay Area Health Task Force in 1986.[2(p2)] That study estimated that 24% to 37% of San Franciscans younger than 65 years are uninsured.

Knowing the potential physician component of the undercompensated and uncompensated care problem enables the Bay Area Health Task Force to begin the process of developing a "community compact," which it describes as "a negotiated agreement between the parties affected by a problem, who agree on the steps each can take to contribute to its solution."[2(pp3-4)]

Between July 1, 1983, and June 30, 1984, hospitals in San Francisco indicated that they incurred just under $200 million in uncompensated care represented by bad debt or charity care (30% or $61.2 million), Medicare contractual allowances ($95.3 million), and Medi-Cal contractual allowances ($42.9 million).[2(p2)] The SFMS survey results emphasize the equally enormous contribution physicians make in providing care to those who cannot pay full fee or pay at all. Based on survey findings, 9% of the value of all services provided in the average medical practice is charity care, 15% is written off as uncompensated care, and another 15% of charges is discounted for Medicare and Medi-Cal patients. Consequently, physicians perceive that a total of 39% of their average potential gross is deliberately provided at no charge, is uncollectible as uncompensated care, or is discounted to government-subsidized patients.

The magnitude of the undercompensated and uncompensated care issue is significant. Approaches to solutions being considered by the Bay Area Health Task Force include both consumer- and provider-oriented approaches, such as:

- Expanding private insurance,
- Creating a state risk-sharing pool,
- Enrolling in prepaid plans,
- Expanding Medi-Cal coverage to include medically indigent adults,
- Establishing payments for services to specific populations,
- Creating a state catastrophic health insurance program,
- Making direct grants to providers,
- Creating earmarked revenue pools,
- Adjusting provider rates.[2(p4)]

A survey of small businesses being undertaken by the Task Force will determine the level of health insurance offered by small employers, clearly define the barriers to offering coverage, and identify the influence of each barrier on the decision to offer or purchase insurance coverage. Similarly, a telephone survey of the working uninsured is intended to delineate the characteristics and subpopulations of this group. Such an approach recognizes that the underinsured and uninsured are not necessarily composed of indigent persons but may be the working poor and even the working well-off (whose employers do not provide insurance coverage) and the self-employed who do not personally choose to use a portion of their incomes to purchase health insurance coverage. The risk of catastrophic illness is one each of these last two groups presently appears willing to take.

The ultimate goal of the task force is to develop a series of health care coverage options that are consistent with enrolling the working uninsured in affordable health care plans. While the burden of caring for the medically indigent may be unevenly distributed among individual physicians and hospitals, the results of the SFMS survey emphasize that physicians generally perceive their own contributions to be large. Moreover, $51,000 in charity or uncompensated care is a substantial individual contribution to a serious societal problem. Federal and state public policymakers critical of physicians' charges must consider their own responsibility for limiting access to care for the medically needy and shifting the cost of care for indigent persons to local public and private pay sectors.

The survey shows that medical providers must cooperate with community, health, and government interests to address the needs of underinsured and uninsured, to see that the contributions of physicians in meeting those needs do not go unrecognized, and to encourage more equitable ways of sharing the burden for such care.

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2. Health Care for the Uninsured and Underinsured: A San Francisco Challenge. Stanford, Calif, Stanford Research Institute International Study for the Bay Area Health Task Force, July 1986

Information

Drugs to Induce Hypotension

RICHARD J. SPERRY, MD
Salt Lake City

EARLY STUDIES OF HEMODYNAMICS during induced hypotension focused principally on global cardiovascular indices such as cardiac output and systemic vascular resistance, whereas regional blood flow and tissue oxygenation received little consideration. New laboratory techniques such as the radiolabeled microsphere and diffusable radioactive tracer methods for determining regional blood flow and microelectrodes for measuring tissue oxygen tension allow investigators to define the influences of the various deliberate hypotensive techniques more precisely. Such advances may have important implications for clinical practice because significant alterations in organ and suborgan regional blood flow can be obscured when only global indices are measured.

None of the common agents—adenosine triphosphate (ATP), sodium nitroprusside, and nitroglycerin—are associated with a decreased blood flow to any vital organ bed during hypotension to 50 mm of mercury, but sodium nitroprusside and ATP may be associated with decreased splanchnic blood flow. Tissue oxygenation is another matter.

Blood flow and tissue oxygenation have been measured in muscle microcirculation during deliberate hypotension with sodium nitroprusside and nitroglycerin.[1] Sodium nitroprusside was found to dilate the precapillary arterioles but not the venules, resulting in a greater than 50% reduction in the arteriolar-venular pressure gradient for microvascular flow. These results suggest that capillary blood flow may be decreased during nitroprusside-induced hypotension and supports the finding of tissue hypoxia during such hypotension. In contrast, nitroglycerin infusion was associated with dilation of both arterioles and venules and an unchanged tissue oxygen tension (Po_2). Thus, striated capillary blood flow is maintained better during hypotension induced with nitroglycerin than during that using sodium nitroprusside.

Brain oxygenation during hypotension was studied by several investigators. Isoflurane, adenosine, and sodium nitroprusside were all shown to decrease brain oxygen tension during typical deliberate hypotension in sheep or rats and during deep hypotension in pigs. Brain metabolism is least altered with the administration of isoflurane and most altered with that of adenosine. A significant decrease in the sagittal sinus Po_2, accompanied by cerebral acidosis and lactate accumulation, has been reported during adenosine-induced hypotension. One investigator has reported that of the three agents isoflurane, sodium nitroprusside, and 2-chloroadenosine—a stable analog of adenosine—2-chloroadenosine most alters the pattern of brain oxygenation.[2]

These results in animals suggest that deliberate hypotension should be used with caution in humans, for they suggest that the margin of safety for brain oxygenation may be compromised to some degree by these agents. Adenosine use may be associated with the poorest brain oxygenation.

Spinal cord blood flow during hypotension and spinal distraction have also received recent attention. Using trimethaphan camsylate has been shown to decrease spinal cord blood flow to half its normotensive value after hypotension is established. Both nitroglycerin- and nitroprusside-induced hypotension, however, are associated with spinal cord blood flow equal to the normotensive value. Longitudinal spinal distraction does not alter spinal cord blood flow from the hypotensive value for any of of the agents.[3]

Thus, although deliberate hypotension has been used with considerable success in humans, it is not without significant and potentially detrimental effects on regional blood flow and tissue oxygenation under some conditions. It appears that each hypotensive agent has specific peripheral vascular and regional hemodynamic actions and that some agents may be superior in terms of organ blood flow and tissue oxygenation. These data indicate that nitroglycerin may be the drug of choice for inducing hypotension during a nonneurologic surgical procedure. Nitroglycerin, however, is not always effective in decreasing arterial blood pressure to the desired level, and another drug may be used in place of or to supplement its use. Both isoflurane and nitroprusside are appropriate supplements or additions if one keeps the above concepts in mind. Nitroglycerin use may also require significant fluid therapy if preload and cardiac output are to be maintained.

Neurologic operations have the additional requirements of attention to decreased intracranial compliance and the provision of a relaxed brain for surgical access. The use of nitroglycerin has a negative effect on both of these requirements. Isoflurane and nitroprusside are therefore the hypotensive agents of choice during neurosurgical procedures.

In summary, the data for tissue oxygen tension suggest that essentially all of the hypotensive techniques decrease brain tissue oxygenation when hypotension is profound. Thus, deliberate hypotension should be used with caution, with careful patient selection, and with meticulous attention to blood pressure control throughout the period of hypotension. When a clear indication for induced hypotension exists, several relative contraindications should be considered such as coronary artery disease or other cardiac disease in which oxygen delivery would be compromised by hypotension, cerebrovascular and peripheral vascular disease, hypovolemia or anemia, and renal or hepatic dysfunction. The autoregulatory shifts that accompany chronic hypertension must also be considered. Monitoring for induced hypotension should include an arterial line for continuous blood pressure and gas tension monitoring. If a large blood loss or fluid shifts are anticipated, a central line for pressure monitoring and a bladder catheter for urinary output are essential.

(Sperry RJ: Drugs to induce hypotension. West J Med 1988 Sep; 149:362)

From the Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City.

This article was sponsored by the Advisory Panel to the Section on Anesthesiology of the California Medical Association Division of Scientific and Educational Activities.

Reprint requests to Richard J. Sperry, MD, Department of Anesthesiology, University of Utah School of Medicine, 50 N Medical Dr, Salt Lake City, UT 84132.

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2. Seyde WC, Longnecker DE: Cerebral oxygen tension in rats during deliberate hypotension with sodium nitroprusside, 2-chloroadenosine, or deep isoflurane anesthesia. Anesthesiology 1986; 64:480-485

3. Spargo PM, Tait AR, Knight PR, et al: Effect of nitroglycerine-induced hypotension on canine spinal cord blood flow. Br J Anaesth 1987; 59:640-647

A NEW H_2 Antagonist

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Brief Summary. Consult the package insert for prescribing information.

Indications and Usage: Axid is indicated for up to eight weeks for the treatment of active duodenal ulcer In most patients, the ulcer will heal within four weeks

Axid is indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg h s after healing of an active duodenal ulcer The consequences of continuous therapy with Axid for longer than one year are not known

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug and should be used with caution in patients with hypersensitivity to other H_2-receptor antagonists

Precautions: *General*—1 Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy

2 Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency

3 Pharmacokinetic studies in patients with hepatorenal syndrome have not been done Part of the dose of nizatidine is metabolized in the liver In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects

Laboratory Tests—False-positive tests for urobilinogen with Multistix® may occur during therapy with nizatidine

Drug Interactions—No interactions have been observed between Axid and theophylline, chlordiazepoxide, lorazepam, lidocaine, phenytoin, and warfarin Axid does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system, therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b i d , was administered concurrently

Carcinogenesis, Mutagenesis, Impairment of Fertility—A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa In a two-year study in mice, there was no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high dose males compared to placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used The female mice were given a dose larger than the maximum tolerated dose, as indicated by excessive (30%) weight decrement compared to concurrent controls, and evidence of mild liver injury (transaminase elevations) The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery is not considered evidence of a carcinogenic potential for Axid

Axid was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, and the mouse lymphoma assay

In a two-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny

Pregnancy—Teratogenic Effects—Pregnancy Category C—Oral reproduction studies in rats at doses up to 300 times the human dose, and in Dutch Belted rabbits at doses up to 55 times the human dose, revealed no evidence of impaired fertility or teratogenic effect, but, at a dose equivalent to 300 times the human dose, treated rabbits had abortions, decreased number of live fetuses, and depressed fetal weights On intravenous administration to pregnant New Zealand White rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous edema in one fetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in one fetus There are, however, no adequate and well-controlled studies in pregnant women It is also not known whether nizatidine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers—Nizatidine is secreted and concentrated in the milk of lactating rats Pups reared by treated lactating rats had depressed growth rates Although no studies have been conducted in lactating women, nizatidine is assumed to be secreted in human milk, and caution should be exercised when nizatidine is administered to nursing mothers

Pediatric Use—Safety and effectiveness in children have not been established

Use in Elderly Patients—Ulcer healing rates in elderly patients are similar to those in younger age groups The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups Age alone may not be an important factor in the disposition of nizatidine Elderly patients may have reduced renal function

Adverse Reactions: Clinical trials of nizatidine included almost 5,000 patients given nizatidine in studies of varying durations Domestic placebo-controlled trials included over 1,900 patients given nizatidine and over 1,300 given placebo Among the more common adverse events in the domestic placebo-controlled trials, sweating (1% vs 0 2%), urticaria (0 5% vs <0 01%), and somnolence (2 4% vs 1 3%) were significantly more common in the nizatidine group A variety of less common events was also reported, it was not possible to determine whether these were caused by nizatidine

Hepatic—Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients possibly or probably related to nizatidine In some cases, there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L), and in a single instance, SGPT was greater than 2,000 IU/L The overall rate of occurrences of elevated liver enzymes and elevations to three times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo-treated patients All abnormalities were reversible after discontinuation of Axid

Cardiovascular—In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in two individuals administered Axid and in three untreated subjects

Endocrine—Clinical pharmacology studies and controlled clinical trials showed no evidence of antiandrogenic activity due to Axid Impotence and decreased libido were reported with equal frequency by patients who received Axid and by those given placebo Rare reports of gynecomastia occurred.

Hematologic—Fatal thrombocytopenia was reported in a patient who was treated with Axid and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs

Integumental—Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients Rash and exfoliative dermatitis were also reported.

Other—Hyperuricemia unassociated with gout or nephrolithiasis was reported

Overdosage: There is little clinical experience with overdosage of Axid in humans If overdosage occurs, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy Renal dialysis for four to six hours increased plasma clearance by approximately 84%

Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal Intravenous LO_{50} values in the rat and mouse were 301 mg/kg and 232 mg/kg respectively PV 2091 AMP [041288]

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CONTINUING MEDICAL EDUCATION

(Continued from Page 284)

September 28-October 1—**2nd Annual AIDS Conference.** San Francisco Department of Health at Civic Auditorium and San Francisco Hotel. Wed-Sat. $225. Contact: 1988 National AIDS Conference, c/o Krebs Convention Management Services, 555 De Haro St, Ste 200, San Francisco 94107. (415) 255-1297.

October 7-9—**Nutrition.** Center for Health Education at Hyatt Regency, Long Beach. Fri-Sun. Contact: Center for Health Education, 2801 Atlantic Ave, PO Box 1428, Long Beach 90801-1428. (213) 595-3811.

October 8-12—**American Academy of Ophthalmology Annual Meeting: 1988.** American Academy of Ophthalmology at Las Vegas Convention Center. Sat-Wed. Contact: American Academy of Ophthalmology, PO Box 7424, San Francisco 94120-7424. (415) 561-8500.

October 10-14—**Current Topics in Occupational Medicine.** UCSF at Cathedral Hill Hotel, San Francisco. Mon-Fri. 40 hrs. $550. Contact: UCSF.

October 11-14—**Intervention Training.** Monterey Community Hospital Recovery Center, Monterey Conference Center. Tues-Fri. $250. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

October 12—**18th Annual Respiratory Symposium.** Enloe and Chico Community Hospitals at Enloe Hospital, Chico. Wed. 6 hrs. Contact: Linda Morgado, Enloe Hospital Medical Staff. (916) 891-7300 ext 7375.

October 13-16—**Primary Care and the Occupational Physician.** Western Occupational Health Conference at Irvine Marriott. Thurs-Sun. Contact: Bob Massaro, Executive Director, 2600 Garden Rd, No 208, Monterey 93940. (408) 649-6544.

October 15—**Office Psychiatry and the Primary Care Physician.** UCLA at Century Plaza Hotel, Century City. Sat. 6 hrs. $35. Contact: UCLA.

October 15-18—**Infectious Diseases: Part I of II.** EPIC Expeditions at Napa Valley. Sun-Tues. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 19-22—**Infectious Diseases: Part II.** EPIC Expeditions at Sonoma Valley. Wed-Sun. 12 hrs. Contact: EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

October 20-22—**What the Clinician Should Know About the Treatment of Chemical Dependence: A Review and Update for Physicians.** California Society for the Treatment of Alcoholism and Other Drug Dependencies at Los Angeles Airport Marriott. Thurs-Sat. 19 hrs. $350. Contact: Gail Jara, California Society. 3803 Broadway, Oakland 94611. (415) 428-9091.

October 20-22—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Mark Hopkins Hotel, San Francisco. Thurs-Sat. 15 hrs. $365. Contact: UCSF.

October 25—**Sexual Addiction and Chemical Dependency: The Hidden Connection.** Institute for Addiction Studies at Health Education Center, Oakland. Sat. $55. Contact: Stephanie Ross, MPI/CDRH, 435 Hawthorne Ave, Oakland 94609. (415) 652-7000.

October 27-30—**Clinical Nutrition.** UCD at Sonoma Valley. Thurs-Sun. Contact: UCD.

October 31-November 3—**Intervention Workshop.** McDonald Center for Alcoholism and Drug Addiction Treatment at La Valencia Hotel, La Jolla. Mon-Thurs. 27 hrs. $250. Contact: Nomi Feldman, Conference Coordinator, 3770 Tansy St, San Diego 92121. (619) 453-6222.

November 4-5—**UCD Multi-Specialty Update: Medical Advances of the 80's.** UCD at Sacramento. Fri-Sat. Contact: UCD.

November 10-13—**Sexual Literacy: What is it? What do we know? What do we need to know? Whose responsibility is it?** The Society for the Scientific Study of Sex at the Cathedral Hill Hotel, San Francisco. Thurs-Sun. Contact: Bernard Goldstein, San Francisco State University, Biology Dept., 1600 Holloway Ave., San Francisco, 94132. (415) 338-1548.

December 1-3—**American Back Society Fall Symposium on Back Pain.** American Back Society at Hyatt Regency, San Francisco. Thurs-Sat. 19 hrs. Contact: American Back Society, 2647 E 14th St, Ste 401, Oakland 94601. (415) 536-9929.

December 9-10—**American Academy of Pain Medicine: 5th Annual Meeting.** American Academy of Pain Medicine at Emerald Hotel, Anaheim. Fri-Sat. Contact: Dr Jack Pinsky, AAPM. (714) 634-6805.

December 24-30—**Advances in Medicine.** Symposium Maui at Royal Lahaina Resort, Kaanapali Beach, Maui, Hawaii. Sat-Fri. 15 hrs. $400. Contact: Joe Harrison, MD, PO Box 10185, Lahaina, Hawaii 96761. (808) 661-8032.

January 19-22—**Health Science Response to Child Maltreatment: 1989.** Children's Hospital & Health Center at Omni Hotel, San Diego. Thurs-Sun. 17 hrs. Contact: Continuing Medical Education Office, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 576-4072.

January 20-22—**Urology and Gynecology for Primary Care Physicians.** UCSD at Hyatt Islandia Hotel, San Diego. Fri-Sun. 13 hrs. Contact: Edith S. Bookstein, UREF, PO Box 2586, La Jolla 92038. (619) 454-3212.

January 20-22—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** Continuing Medical Education Associates at San Diego Princess Resort. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

January 20-22—**Adolescent Medicine for the Practitioner.** Scripps Clinic and Research Foundation at La Jolla Marriott. Fri-Sun. 18 hrs. $225. Contact: Bonny A. Mower, Conference Coordinator, Department of Academic Affairs, 400S, Scripps Clinic and Research Foundation, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 457-8556.

January 29-February 3—**Selected Topics in Family Practice.** Tropical Seminars at King Kamehameha Hotel, Kona, Hawaii. Sun-Fri. 20 hrs. Contact: Tropical Seminars, North Kitsap Medical Center, 20700 Bond Rd NE, Poulsbo, WA 98370-9099. (800) 441-4439.

February 17-19—**Office Gynecology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $345. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 25-March 4—**Update: Controversies in Emergency and Primary Care.** Scripps Memorial Hospital Encinitas at Royal Lahaina Resort, Maui, Hawaii. One week. 21 hrs. $395. Contact: Edith S. Bookstein, AIPE, PO Box 2586, La Jolla 92038. (619) 454-3212.

March 3-5—**Asia Pacific Alzheimer's Disease Conference.** Pacific Islands Geriatric Education Center at Hilton Hawaiian Village, Honolulu, Hawaii. Fri-Sun. 21 hrs. $300. Contact: Katherine Kim, Pacific Islands Geriatric Education Center, 347 N Kuakini St, Honolulu, HI 96817. (808) 523-8461.

March 5-8—**Asia-Pacific Osteoporosis Conference.** Kuakini Osteoporosis Center at Hilton Hawaiian Village, Honolulu, HI. Sun-Wed. 25 hrs. $450. Contact: Shirley Kuma, KOC, 347 N Kuakini St, Honolulu, HI 96817. (808) 547-9578.

March 19-22—**Annual Meeting of the Society for Adolescent Medicine.** Society for Adolescent Medicine at San Francisco. Sun-Wed. Contact: Edie Moore, 10727 White Oak Ave, Ste 101, Granada Hills 91344. (818) 368-5996.

IDAHO

September 2-5—**Strategies for Fitness and Health Promotion.** University of Arizona College of Medicine, Department of Family and Community Medicine, and Epic Expeditions at Sun Valley. 12 hrs. Contact: Kathy Rairigh, EPIC Expeditions, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 364)

September 17-18—**NM Chapter, American College of Surgeons Scientific Meeting.** Ramada Classic, Albuquerque. Contact: Dorothy Welby, (505) 266-7868.

September 22-24—**Primary Care Update '88.** UNM Conference Center, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 1—**Breastfeeding in the 21st Century: Concepts, Controversies and Advanced Practice.** Albuquerque. Ramada Hotel Classic. Contact: Lact-Natch Breastfeeding Clinic, 3620 Wyoming NE, #102, Albuquerque 87111. (505) 298-6243.

October 6-8—**Management of Radiation Accidents.** Sheraton Old Town Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 7-8—**4th Annual Balloon Fiesta Lung Conference.** Fri-Sat. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

October 18-21—**Epidemiologic & Methodologic Problems in Determining Nutritional Status of Older Persons.** Sheraton Old Town Hotel, Albuquerque. Tues-Fri. Contact: UNM SOM, Office of CME, (505) 277-3942.

October 28-29—**New Mexico Medical Society Interim Meeting** and **Loss Control Seminar,** Physicians Mutual Liability Insurance Co. Journal Center Pyramid Holiday Inn, Albuquerque. Fri-Sat. Contact: New Mexico Medical Society, 303 San Mateo NE, Albuquerque 87108. (505) 266-7868.

November 11-13—**Adolescent Medicine.** Hilton Inn, Las Cruces. Fri-Sun. Contact:Marilyn Stark, NM Chapter, American Academy of Pediatrics, 7605 Mountain NE, Albuquerque 87110. (505) 265-7431.

December 1-3—**American College of Physicians—New Mexico Scientific Meeting.** Hilton Hotel, Albuquerque. Thurs-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

December 9-10—**Trauma Update '88.** Clarion Four Seasons Hotel, Albuquerque. Fri-Sat. Contact: UNM SOM, Office of CME, (505) 277-3942.

February 24-26—**17th Annual New Mexico Thoracic Society Lung Disease Conference.** Taos. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 217 Truman NE, Albuquerque 87108. (505) 265-0732.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wed—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept of Internal Medicine, Univ of Utah, (801) 581-7606.

* * *

September 21-24—**Utah Medical Association Annual Meeting—Featuring Nine Specialty Sessions** (Sponsor: UMA). Wed-Sat. University Park Hotel, Salt Lake City. Contact: Jeanne Crippen, (801) 355-7477.

(Continued on Page 366)

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it, however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of Yocon® 1/12 gr. 5.4 mg in bottles of 100's NDC 53159-001-01 and 1000's NDC 53159-001-10.

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 365)

September 22-24—**Central Association of Obstetricians & Gynecologists** (Sponsor: UUMC). Thurs-Sat. 10.5 hrs. Salt Lake City Marriott. Contact: (801) 333-0988.

September 30—**Update in Gastroenterology** (Sponsor: UUMC). Fri. 6 hrs. Salt Lake Red Lion. Contact: (801) 581-8664.

October 13-14—**Laser Surgery: Gastroenterology** (Sponsor: UUMC). Thurs-Fri. 12 hrs. Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

November 17-18—**Laser Surgery: Gastroenterology** (Sponsor: UUMC). Thurs-Fri. 11 hrs. Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

December 1-2—**Laser Surgery: Angioplasty** (Sponsor: UUMC). Thurs-Fri. 11 hrs. Salt Lake City. Contact: Mike Johnson, (801) 581-3293.

January 6-8—**Hip and Knee Bioskills Workshop** (Sponsor: UUMC). Fri-Sun. 15 hrs. Snowbird. Contact: (801) 581-8664.

January 12-14—**Arthroscopic Surgery** (Sponsor: UUMC). Thurs-Sat. Phoenician Resort, Scottsdale, Arizona. Contact: (801) 581-7601.

January 14-21—**Special Problems in Athletic Injuries and Trauma** (Sponsor: UUMC). One week. Aston Genesis Resort, Park City. Contact: (801) 581-8664.

February 5-10—**A Practical Approach to Modern Chest and Musculoskeletal Radiology** (Sponsor: UUMC). Sun-Fri. Snowbird. Contact: (801) 581-7553.

February 7-10—**Family Practice Refresher Course** (Sponsor: UUMC). Tues-Fri. Red Lion Inn, Salt Lake City. Contact: (801) 581-8635.

February 12-17—**Update in Clinical Microbiology and Immunology** (Sponsor: UUMC). Sun-Fri. The Yarrow, Park City. Contact: (801) 581-8664.

February 22-25—**Pediatric Emergency Medicine** (Sponsor: UUMC). Wed-Sat. Salt Lake City Marriott. Contact: (801) 521-1311.

February 22-25—**Rigid Fixation and Craniofacial Anomalies** (Sponsor: UUMC). Wed-Sat. Snowbird. Contact: (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

AHA: American Heart Association, Utah Affiliate, 645 E 400 South, Salt Lake City 84102. (801) 322-5601.

BYUHS: Brigham Young University Health Services, McDonald Student Health Center, Brigham Young University, Provo 84602. (801) 378-2771.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 S 300 East, Salt Lake City 84101. (801) 262-3461.

DMC: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 673-9681.

HCH: Holy Cross Hospital, 1045 E First South, Salt Lake City 84102. (801) 350-4744.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd, Ogden 84409. (801) 399-4141.

MVH Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.

144: 144th Evacuation Hospital, PO Box 8000, Salt Lake City 84108. (801) 524-3924.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave, Salt Lake City 84103. (801) 363-1221.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

SMH St Mark's Hospital, 1200 E 3900 South, Salt Lake City 84117. (801) 268-7111.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUMC: University of Utah Medical Center, 50 N Medical Dr, Salt Lake City 84132. (801) 581-2258.

UVRMC: Utah Valley Regional Medical Center, 1034 N Fifth West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

VVMC: Valley View Medical Center, 595 S 75 East, Cedar City 84720. (801) 586-6587.

February 26-March 3—**A Practical Approach to Modern Chest and Musculoskeletal Radiology** (Sponsor: UUMC). Sun-Fri. Park City. Contact: (801) 581-7553.

March 1-4—**Update in Maternal Fetal Medicine** (Sponsor: UUMC). Wed-Sat. Contact: (801) 581-5501.

March 5-11—**Advances in Internal Medicine** (Sponsor: UUMC). Sun-Sat. Snowbird. Contact: (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

September 17-24—**Effective Management of Common Sports Injuries.** San Juan Islands. Sat-Sat. Contact: Kathy Rairigh, EPIC Expeditions, (208) 788-4995.

September 19-20—**Focus: Critical Care 1988.** Tacoma. Mon-Tues. Contact: Tacoma General Hospital. (206) 594-1268.

September 22-23—**Non-Ionizing Radiation.** Seattle. Thurs-Fri. Contact: U/W, (206) 543-1069.

September 22-24—**Orthopedic Biomechanics.** Seattle. Thurs-Sat. Contact: VMMC.

October 12—**Management of Chemical Hazards.** Seattle. Mon. Contact: U/W, (206) 543-1069.

October 27-28—**Annual Current Concepts in Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W, Maria Lilja, (206) 543-1050.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

September 14-18—**Wilderness Medicine '88—Annual Meeting of the Wilderness Medical Society.** Jackson Lake Lodge, Grand Teton National Park. Wed-Sun. Contact: Diag Simpkins, Wilderness Medical Society, PO Box 397, Point Reyes Station, CA 94956. (415) 663-9107.

September 17-18—**Medicine Update.** Creighton University School of Medicine at Inn at Jackson Hole, Teton Village. Sat-Sun. 10 hrs. Contact: Division of CME, Creighton University School of Medicine, Omaha, NE 68178. (800) 548-2633. ◆

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Specialty	Composite* Insurance Companies	CAP/MPT	Savings with CAP/MPT	Composite* Insurance Companies	CAP/MPT	Savings with CAP/MPT
Psychiatry	$ 5,100	$ 2,365	54%	$ 3,789	$ 2,052	46%
Pediatrics	7,357	2,365	68%	6,208	2,052	67%
Urology	18,571	13,735	26%	14,560	11,776	19%
Anesthesiology	19,704	13,735	30%	16,299	11,776	28%
General Surgery	30,841	17,853	42%	22,388	15,306	32%
Plastic Surgery	31,557	17,853	43%	22,961	15,306	33%
Orthopedic Surgery w/Spinal	39,744	21,971	45%	34,184	18,837	45%
Obstetrics/ Gynecology	49,812	21,971	56%	40,220	18,837	53%

* Insurance company composite rates are averages based upon 4/1/88 rates of The Doctors' Company, 6/1/87 rates of MIEC, 1988 rates of Norcal and SCPIE. Details of source data on request. No costs shown here for San Diego or Imperial County. Other surcharges, credits, reductions may apply. All costs based on mature rate (including retroactive coverage).

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PORTLAND, OREGON. Established, rapidly growing practice seeks BE/BC Internist. Multispecialty group active in private and HMO practice with satellite office. Salary and benefits first two years lead to partnership. Send CV to SMC, 10535 NE Glisan St, Portland, OR 97220, Attn: Dick Hamilton; (503) 256-0594.

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(Continued on Page 372)

THE INSIDE STORY
IN HYPERTENSION

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Because it vasodilates

THE OUTSIDE STORY

UNCOMPROMISED VITALITY

- ☐ Low incidence of fatigue and impotence[7]
- ☐ Preserves exercise tolerance[5]
- ☐ High level of patient acceptance

Trandate Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia.

For references and a complete listing of reported adverse reactions, including incidence at various dosage levels, please see ADVERSE REACTIONS section of the Brief Summary of Prescribing Information on next page.

Please see next page for references and Brief Summary of Prescribing Information.

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References: 1. Malini PL, Strocchi E, Negroni S, et al: Renal haemodynamics after chronic treatment with labetalol and propranolol. *Br J Clin Pharmacol* 1982;13(suppl 1):123S-126S. 2. Pedersen EB, Larsen JS: Effect of propranolol and labetalol on renal haemodynamics at rest and during exercise in essential hypertension. *Postgrad Med J* 1980;56(suppl 2):27-32. 3. Wallin JD: Antihypertensives and their impact on renal function. *Am J Med* 1983;75:103-108. 4. Koch G: Haemodynamic adaptation at rest and during exercise to long-term antihypertensive treatment with combined alpha- and beta-adrenoreceptor blockade by labetalol. *Br Heart J* 1979;41(2):192-198. 5. Feit A, Holtzman R, Cohen M, et al: Effect of labetalol on exercise tolerance and double product in mild to moderate essential hypertension. *Am J Med* 1985;78:937-941. 6. Lund-Johansen P: Short- and long-term (six-year) hemodynamic effects of labetalol in essential hypertension. *Am J Med* 1983;75:24-31. 7. Burris JF, Goldstein J, Zager PG, et al: Comparative tolerability of labetalol versus propranolol, atenolol, pindolol, metoprolol, and nadolol. *J Clin Hypertens* 1986;3:285-293.

TRANDATE® Tablets
(labetalol hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in TRANDATE® Tablets product labeling.

CONTRAINDICATIONS: TRANDATE® Tablets are contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock, and severe bradycardia (see WARNINGS).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta-blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response should be observed closely. If cardiac failure continues despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after a *abrupt* discontinuation of such therapy. When discontinuing chronically administered TRANDATE, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of one to two weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue TRANDATE therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (eg, Chronic Bronchitis and Emphyseme): Patients with bronchospastic disease should, in general, not receive beta-blockers. TRANDATE may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if TRANDATE is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma: Labetalol HCl has been shown to be effective in lowering blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy before major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see PRECAUTIONS: Drug Interactions).

PRECAUTIONS: General: *Impaired Hepatic Function:* TRANDATE® Tablets should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction: On rare occasions, labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incidence of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see ADVERSE REACTIONS).

Laboratory Tests: As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: In one survey, 2.3% of patients taking labetalol HCl in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal antiasthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will

TRANDATE® (labetalol hydrochloride) Tablets

be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for two years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl using dominant lethal assays in rats and mice and exposing microorganisms according to modified Ames tests showed no evidence of mutagenesis.

Pregnancy: *Teratogenic Effects: Pregnancy Category C:* Teratogenic studies were performed with labetalol in rats and rabbits at oral doses up to approximately six and four times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of two to four times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE Tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects are mild, transient, and occur early in the course of treatment. In controlled clinical trials of three to four months' duration, discontinuation of TRANDATE® Tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The following adverse reactions were derived from multicenter, controlled clinical trials over treatment periods of three and four months. The rates, which ranged from less than 1% to 5% except as otherwise noted, are based on adverse reactions considered probably drug-related by the investigator. If all reports are considered, the rates are somewhat higher (eg, dizziness, 20%; nausea, 14%; fatigue, 11%).

Body as a Whole: Fatigue, asthenia, headache. ***Gastrointestinal:*** Nausea (6%), vomiting, dyspepsia, diarrhea, taste distortion. ***Central and Peripheral Nervous Systems:*** Dizziness (11%), paresthesia, drowsiness. ***Autonomic Nervous System:*** Nasal stuffiness, ejaculation failure, impotence, increased sweating. ***Cardiovascular:*** Edema, postural hypotension. ***Respiratory:*** Dyspnea. ***Skin:*** Rash. ***Special Senses:*** Vision abnormality, vertigo.

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, ie, a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. The US therapeutic trials data base for adverse reactions that are clearly or possibly dose-related shows that the following side effects increased with increasing dose: dizziness, fatigue, nausea, vomiting, dyspepsia, paresthesia, nasal stuffiness, ejaculation failure, impotence, and edema.

In addition, a number of other less common adverse events have been reported in clinical trials or the literature:

Cardiovascular: Postural hypotension, including, rarely, syncope. ***Central and Peripheral Nervous Systems:*** Paresthesia, most frequently described as scalp tingling. In most cases, it was mild, transient, and usually occurred at the beginning of treatment. ***Collagen Disorders:*** Systemic lupus erythematosus; positive antinuclear factor (ANF). ***Eyes:*** Dry eyes. ***Immunological System:*** Antimitochondrial antibodies. ***Liver and Biliary System:*** Cholestasis with or without jaundice. ***Musculoskeletal System:*** Muscle cramps, toxic myopathy. ***Respiratory System:*** Bronchospasm. ***Skin and Appendages:*** Rashes of various types, such as generalized maculopapular, lichenoid, urticarial, bullous lichen planus, psoriaform, and facial erythema; Peyronie's disease; reversible alopecia. ***Urinary System:*** Difficulty in micturition, including acute urinary bladder retention.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects: In addition, other adverse effects not listed above have been reported with other beta-adrenergic blocking agents. ***Central Nervous System:*** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on psychometrics. ***Cardiovascular:*** Intensification of AV block (see CONTRAINDICATIONS). ***Allergic:*** Fever combined with aching and sore throat; laryngospasm, respiratory distress. ***Hematologic:*** Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura. ***Gastrointestinal:*** Mesenteric artery thrombosis, ischemic colitis. The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl.

Clinical Laboratory Tests: There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and, more rarely, reversible increases in blood urea.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: DOSAGE MUST BE INDIVIDUALIZED. The recommended *initial* dosage is 100 mg *twice* daily whether used alone or added to a diuretic regimen. After two or three days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every two or three days. The usual *maintenance* dosage of labetalol HCl is between 200 and 400 mg *twice* daily. Before use, see complete prescribing information for dosage details.

April 1988

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(Continued from Page 368)

PHYSICIAN WANTED

INTERNAL MEDICINE. San Francisco bay area—Immediate opening for BC/BE General Internist in large prepaid group practice. Busy outpatient and hospital practice. Medical house staff program. Opportunity for university appointment, teaching, and clinical research. Competitive salary. Generous fringe benefits including paid educational leave, vacation, insurance, retirement. Respond with CV to Joseph Mason, MD, Chief, Department of Medicine, The Permanente Medical Group, 260 International Cir, San Jose, CA 95119.

VENTURA (VENTURA COUNTY). Multispecialty group of 35 physicians has immediate positions available for BC/BE General Internists. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. No investment required. Excellent benefits. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist, 2705 Loma Vista Rd, Ventura, CA 93003.

GENERAL INTERNIST OR BC FAMILY PRACTITIONER. Excellent opportunity to start or relocate in growing resort community in need of another physician. Hospital privilege a must. Will help a motivated individual. L. D. Lamothe, MD, 13120 Palm Dr, Desert Hot Springs, CA 92240.

ONCOLOGIST BC/BE to join multispecialty group near San Francisco. Excellent fringe benefits. Send CV to Dr Gary L. Hillman, Chief, Department of Medicine, The Permanente Medical Group, 1150 Veterans Blvd, Redwood City, CA 94063.

NORTHERN CALIFORNIA. Opportunity for a full-time position in a hospital-based urgent care center. Compensation is $40-45 per hour and malpractice is paid. If you are BE/BC in a primary specialty, we'd like to talk to you. Send your CV to Northern California Emergency Physicians, PO Box 214584, Sacramento, CA 95821 or call us at (916) 486-4414.

FEMALE ORIENTED PRACTICE. Great potential for Family Practitioner or Internist with emphasis on primary care of women (no OB) in a small college town, Rocky Mountain setting. Associate, join or coverage with solo Internist. Must be easy to work with and have good patient rapport. Reply to Number 104, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

ENDOCRINOLOGIST BC/BE, with interest in diabetes, to assume established practice. Join a dynamic group of 10 Internists/Specialists. Outstanding initial guarantees and financial incentives. City of 50,000 is a regional referral center for 250,000. Local recreational and educational opportunities abound in this Pacific Northwest city with sunbelt climate. Send CV to Chris Nauta, Administrator, Internal Medicine Associates of Yakima, Inc, PS, 316 Holton Ave, Yakima, WA 98902.

INTERNAL MEDICINE. Full-time position for a BC/BE Internist in an 18 resident, seven faculty, rural Family Medicine Program affiliated with the University of California, Davis. Duties will include supervising residents on the medical ward and in the ICU/CCU areas. Excellent salary. Send inquiries with CV to J. E. Hughell, MD, Director, Family Practice Residency Program, Merced Community Medical Center, PO Box 231, Merced, CA 95340; (209) 385-7172. EOE.

FAMILY PRACTICE (GERIATRICS). Full-time faculty position for a BC Family Physician with a special interest in Geriatrics in an 18 resident, seven faculty, rural program affiliated with the University of California, Davis. Large clinical component, including out-patient care and supervising residents on in-patient services and in convalescent hospitals. Send inquiries with CV to J. E. Hughell, MD, Director, Family Practice Residency Program, Merced Community Medical Center, PO Box 231, Merced, CA 95340; (209) 385-7172. EOE.

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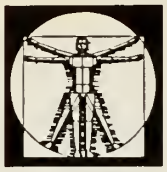

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PHYSICIANS WANTED

FAMILY PRACTICE. Steinbeck country, BC/BE Family Practitioner to join dynamic group; includes hospital care, OB, shared call. Spanish helpful. Many visiting consultants, good guarantee with chance for early partnership. Many fringes. One hour to Monterey, three hours to San Francisco. Call or write: Helen Poole, 210 Canal St, King City, CA 93930; (408) 385-5471.

VENTURA (VENTURA COUNTY). Multispecialty group of 35 physicians has immediate positions available for BC/BE Internist/Pulmonologist. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Internist/Pulmonologist, 2705 Loma Vista Rd, Ventura, CA 93003.

VENTURA (VENTURA COUNTY). Multispecialty group of 35 physicians has immediate positions available for BC/BE Family Practitioner. This growth oriented group is located on the California coast, 60 miles north of Los Angeles. Guaranteed salary plus incentives. Excellent benefits. No investment required. City is a great place to raise a family in a clean environment. Send résumés to Recruitment, Family Practitioner, 2705 Loma Vista Rd, Ventura, CA 93003.

PORTLAND, OREGON. Practice opportunities available for BC/BE Family Practitioners and General Internists. Full specialty back-up; call sharing available. Affiliate with progressive community hospital. Practice assistance includes salary guarantee, rent, relocation allowance. Send CV to Cynthia Lacro, Woodland Park Hospital, 10300 NE Hancock St, Portland, OR 97220; (503) 257-5671.

FAMILY PHYSICIANS. BC/BE, full- and part-time positions available with Obstetrics optional, to work with multispecialty group practice in the Seattle area. Attractive salary and benefits. Send CV to Pacific Health Associates, Northgate Clinic, 10416 5th Ave NE, Seattle, WA 98125, Attn: Peter Hohn, MD.

WYOMING. Immediate opening for experienced Emergency Room Physician. Competitive salary, occurrence liability insurance, excellent working conditions, new facility, low to moderate volume. Excellent outdoor recreation, hunting, fishing, one hour from nationally known ski slopes and Salt Lake City. Please call Richard Rosenthal, MD, in Evanston, Wyoming at (307) 789-3636 or write Evanston Regional Hospital, 190 Arrowhead Dr, Evanston, WY 82930.

PHYSICIANS WANTED

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HEMATOLOGIST/ONCOLOGIST, WASHINGTON STATE. BC/BE immediate opportunity to take over established practice within the Hematology/Oncology (three and one-half physician) Division of the Rockwood Clinic, a 60 member multispecialty group. Competitive salary and benefits leading to early shareholder status. Spokane (metropolitan population 350,000) offers affordable housing, excellent schools, cultural activities, and unlimited outdoor recreation. Send CV to Colleen Mooney, Recruitment Coordinator, Rockwood Clinic, TAF C-13, Spokane, WA 99220-4013; (509) 448-1304.

FAMILY PRACTITIONER needed for rural underserved area in Hawaii. Full-time position in nonprofit community health clinic. No OB, hospitalizations optional. Desire dedicated person to work in multicultural setting. Contact Alan Chun, MD, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792; (808) 696-7081.

INTERNIST. San Francisco bay area HMO seeks BC/BE Internist to join dynamic multispecialty group. Excellent salary and fringe benefits. Send CV and references to Dr Michael Getzell, Kaiser Permanente, 27400 Hesperian Blvd, Hayward, CA 94545.

(Continued on Page 374)

SURGEONS AND INTERNISTS:

THE ARMY NEEDS PHYSICIANS PART-TIME.

The Army Reserve offers you an excellent opportunity to serve your country as a physician and a commissioned officer in the Army Reserve Medical Corps. Your time commitment is flexible, so it can fit into your busy schedule. You will work on medical projects right in your community. In return, you will complement your career by working and consulting with top physicians during monthly Reserve meetings and medical conferences. You will enjoy the benefits of officer status, including a non-contributory retirement annuity when you retire from the Army Reserve, as well as funded continuing medical education programs. A small investment of your time is all it takes to make a valuable medical contribution to your community and country. For more information,

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Colorado, Montana, N. Dakota, S. Dakota and Wyoming — (303) 361-8841

ARMY RESERVE. BE ALL YOU CAN BE.

(Continued from Page 372)

PHYSICIANS WANTED

RADIOLOGIST, BC/BE for a 120-bed hospital. California license. General Radiology including CT, ultrasound, and nuclear medicine. Send CV to Dr H. Hashim, c/o Delano Regional Medical Center, PO Box 460, Delano, CA 93216.

OCCUPATIONAL/FAMILY PRACTICE. Extensive Occupational/Family Practice network of rapidly growing medical center in Pacific northwest has excellent full/part-time opportunities throughout California and Washington (Seattle/Tacoma). Regular hours and a balanced professional/personal lifestyle. Attractive salary/incentives/benefits/malpractice. Current state license. Prior Occupational/Family Practice experience. Join our dynamic team of professionals. Contact Director, Personnel, ReadiCare/CHEC, 446 Oakmead Pkwy, Sunnyvale, CA 94086; (408) 737-8531, (800) 237-3234.

NEW MEXICO communities have excellent private practice opportunities available for the following specialties: BC/BE Family Practitioners, Internists, OB/GYNs, and Orthopaedic Surgeons. Financial assistance available on all opportunities. For further information, please submit CV to Bill Norris or Rita Longino, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666; or call 1 (800) 545-4030, ext 8300.

HAVE THE BEST OF BOTH WORLDS. Rural group practice, easy commute 40 minutes to larger city. Excellent clinical practice with option for close ties to academic hospitals and part-time teaching. BC/BE Family Practitioner to join with three Family Practitioners/OB/GYN/two Pediatricians/General Surgeon, adjacent to hospital. Attractive salary/incentives. Excellent outdoor recreational opportunities. Send CV to Peter Bauer, MD, Medical Director, Family Practice Group, 255 South 1st East, Tooele, UT 84074; (801) 882-0423.

PRIMARY CARE—FAMILY PRACTICE OR INTERNAL MEDICINE. BE/BC staff physicians for primary care clinic on Monterey Peninsula, California. Daytime hours, professional liability insurance procured for you, possible management position. Call Scott Caldie at (800) 528-0396. Coastal Government Services, PO Box 15066, Durham, NC 27704.

SURGEON OPPORTUNITY. Immediate opening for General Surgeon in rural Nebraska. BC/BE. Must be licensed in Nebraska. Excellent benefits. Great hunting and fishing. Wallace & Panzer, MD, PC, 807 N. Ash St, Gordon, NE 69343; 1 (308) 282-1164.

SACRAMENTO. General Internist with or without subspecialty for busy, well-established Internal Medicine group. Send CV to David H. Lehman, MD, 2801 K St, Ste 520, Sacramento, CA 95816.

FAMILY PRACTICE/GENERAL PRACTICE PHYSICIAN, two positions open with northern Sacramento Valley Rural Health Project in northern California. 1. One physician needed at Lindhurst Family Health Center (five miles south of Marysville, California)—busy clinic with three physicians and one family nurse practitioner. 2. Another physician needed at Oroville Family Health Center in Oroville, California (30 miles north of Marysville). This clinic has one physician and one physician assistant at present, but needs another physician. Phone Mr Louie Campos, Executive Director, (916) 743-6638, or Herman Gray, MD, Medical Director, (916) 865-5544; 4941 Olivehurst Ave, Olivehurst, CA 95961.

CALIFORNIA—GENERAL SURGERY. Full range of medicine. Solo, partnership, or group. Nice community surrounded by the mountains. Easy equal access to San Francisco, Los Angeles, beach or skiing. No smog or fog, just great weather. Excellent financials and support. Contact Jeffrey Gowan at (800) 288-1210 or send CV to 500 N. Newport Blvd, Ste 204, Newport Beach, CA 92663.

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CALIFORNIA. BE/BC Internist to join staff of eight Internists in 14 physician multispecialty group located in central San Joaquin Valley. Competitive starting salary and full benefits. Excellent living and practice environment. Send CV to Frank Kelley, MD, Kaweah Medical Group, 222 W. Willow, Visalia, CA 93291.

ORTHOPEDIC SURGEON. Immediate opening for BC/BE Surgeon to join two physician Orthopedic Surgery practice in San Jose, California. Staff and patient load is at level for three physicians. Excellent location across the street from medical center. Competitive compensation, malpractice, car expense, and generous benefit package provided. Send CV to Anthony Wax, Administrator, San Jose Orthopedic Medical Group, 25 N. 14th St, Ste 700, San Jose, CA 95112; or call Dr Paul Swartz at (408) 294-2714.

INTERNAL MEDICINE OPPORTUNITY. Immediate opening for an inpatient-based General Internist serving a unique role in a private, not-for-profit, comprehensive medical rehabilitation center. Salary and benefits are competitive. If interested, please send your CV to Dr Gary Okamoto, Medical Director, REHAB Hospital, 226 N. Kuakini St, Honolulu, HI 96817.

THE GALLUP-THOREAU-GRANTS HEALTH CARE SYSTEM is recruiting for two medical provider positions for their facility in Grants, New Mexico. 1: Family Practice/General Practice Physician with six months of Obstetrical training, willing to work with OB/GYN and Pediatrician. 1: OB/GYN Physician, willing to work with a Family Practice/General Practice Physician and Pediatrician. For more information, please contact Ms Liz Baca or Mr Monty Small at (505) 863-3663 or write to Gallup-Thoreau-Grants Health Care System, PO Box 1708, Gallup, NM 87305.

INTERNAL MEDICINE, PEDIATRICIAN, AND OB/GYN NEEDED. San Ysidro Health Center, a comprehensive multispecialty clinic in south San Diego County, seeks an Internist, a Pediatrician, and an OB/GYN for full-time work. Competitive salary, excellent benefits. Send résumé to Norma Diaz, 4004 Beyer Blvd, San Ysidro, CA 92073; (619) 428-4463, ext 361.

(Continued on Page 376)

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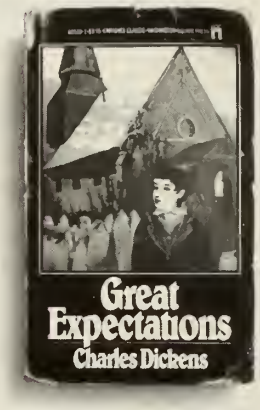

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MEDICAL PROGRAM DIRECTOR

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The County of Orange, Health Care Agency in Southern California, is seeking a Medical Director to oversee the expanding medical component of the Correctional Medical Services program. The selected Physician will direct a medical care delivery system, supervise other Physicians and Nurse Practitioners, provide medical consultation services for medical and/or ancillary staff, develop medical protocols and represent Correctional Medical Services as a liaison with other County agencies/departments and local health care providers.

Opportunity to work in a dynamic and challenging work environment with a dedicated multi-disciplinary team of health professionals.

Must be a California licensed Physician with five years of increasingly responsible medical and administrative experience. Excellent fringe benefit package. **Send curriculum vitae to Rosie Rivera, Health Care Agency Personnel, 525 N. Sycamore, Santa Ana, CA 92701 or call (714) 834-3035.** Affirmative Action Employer M/F.

(Continued from Page 374)

PHYSICIANS WANTED

SEATTLE, WASHINGTON. Outstanding opportunity to join multispecialty group practice. Full spectrum Family Practice with Obstetrics, associated with 250 bed hospital. Excellent financial package including guaranteed salary, benefits, interviewing and relocation expenses paid. Address inquiries to Dr Rockwell S. Fredrickson, Pacific Medical Center North, 10416 5th Ave NE, Seattle, WA 98125.

GERIATRICS FACULTY POSITION. The University of California, Davis, School of Medicine is recruiting for a full-time faculty position at the Assistant Professor in Residence level to assist in an expanding Geriatric program at UCD. The school has a major commitment to Geriatric Medicine and has already established a Center for Aging and Health. The candidate must be BE/BC in Internal Medicine with appropriate experience in an academic Geriatric/Gerontology program and must qualify for California licensure. A letter outlining research, teaching interests, Geriatric experience, and a CV must be received by October 1, 1988. Send reply to James K. Cooper, MD, Internal Medicine, PCC 3120, 2221 Stockton Blvd, Sacramento, CA 95817. The University of California is an Equal Opportunity/Affirmative Action Employer.

THE ELKO REGIONAL MEDICAL CENTER is presently recruiting a Pediatrician, two Family Practitioners, and a Radiologist to assist in its growing practice. Excellent salary plus production and a comprehensive benefit package which includes profit sharing. Elko, Nevada is a rapidly growing rural community at the base of the Ruby Mountains. Outstanding recreational opportunities and school system, including a community college. Contact: Cherie Atwood, Administrator, 762-14th St, Elko, NV 89801; (702) 738-3111.

PHYSIATRIST, BC, for a position as the Medical Director of a new physical medicine hospital in Sun City, Arizona. Call Mr Randall Sheridan at the Arizona Rehabilitation Center, (602) 972-1153.

PHYSICIANS WANTED

WANTED—PRIMARY CARE PHYSICIANS (General Practitioner, Family Practitioner—Internal Medicine) to work in the Psychiatric setting as a part of a multi-disciplinary team. Salary negotiable. Contact Mr Harvey Hanemoto, 2633 E. 27th St, Oakland, CA 94601; (415) 536-8111, ext 285.

SIX PHYSICIAN PRIMARY CARE GROUP seeks BC/BE Cardiologist for invasive/noninvasive practice in vacation community on Puget Sound. Practice located adjacent to community hospital, which is affiliated with Virginia Mason Medical Center in Seattle. Send CV to Harold R. Clure, MD, Fidalgo Medical Associates, PS, 24th and M Ave, Anacortes, WA 98221; or call (206) 293-3101.

EMERGENCY MEDICINE GROUP seeking career oriented ACLS, ATLS physician for immediate opening. Moderate volume; income $140,000. Great outdoor activities including hunting, fishing, boating, skiing, sailing, camping, and hiking in south central Washington on the Columbia River. Send CV to KEP, PO Box 6192, Kennewick, WA 99336; or call (509) 627-1798.

NEUROSURGEON. BC to work as locum tenens in 175-bed county hospital for a month or less. Paid malpractice. Roger A. Smith, MD, 780 E. Gilbert St, San Bernardino, CA 92404; (714) 387-8016.

PEDIATRIC PARTNERSHIP OPPORTUNITY AVAILABLE in Rocky Mountain community of 18,000 with service area of 50,000. A morning's drive from the Grand Tetons and Yellowstone. Tremendous recreation available including downhill skiing, water activities on neighboring lakes, etc. Outstanding school systems and quality of life. Join existing Pediatrician in growing, expanding practice. Brand new, financially stable hospital. $80,000 minimum net guarantee including all overhead expenses and benefits through guarantee. Call Timothy Donohue, Jackson & Coker, 400 Perimeter Center Terrace, Ste 760 WJM8, Atlanta, GA 30346; 1 (800) 544-1987 or 1 (800) 888-0121.

PHYSICIANS WANTED

PHYSICIANS WANTED IN TEXAS AND OKLAHOMA. Major cities to rural communities. Cardiology, ENT, Family Practice, General Surgery, Internal Medicine, OB/GYN, Oncology, Orthopedic Surgery, Pediatrics, Psychiatry, Radiology, Rheumatology. Excellent quality of life, first year guarantee, etc. Reply with CV or call Armando L. Frezza, Medical Support Services, 8806 Balcones Club Dr, Austin, TX 78750; office: (512) 331-4164; 24 hour FAX (512) 331-6741.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled, Family Practice or Emergency Physician to join highly respected urgent care group with two beautiful Santa Cruz clinics. Committed to high quality care. Nice people, flexible scheduling, comprehensive benefits, including: paid malpractice, group health insurance, long-term disability insurance, no nights, rapid advancement to full partnership in an outstanding place to live. Please send CV to Robert Korns, MD, 6800 Soquel Dr, Aptos, CA 95003 or call (408) 662-3611.

SAN FRANCISCO BAY AREA. Full-time career Emergency Physician wanted for a high volume Emergency Department, 30 minutes south of San Francisco. Emergency Medicine BC/BE mandatory; prefer experienced. Congenial, democratic group of 20 full-time physicians doing some follow-up and minimal overnights. Competitive salary with excellent benefits including three-five weeks paid vacation; seven paid holidays; malpractice, medical, dental and disability insurance; corporate shareholder in three years. Send CV or contact Drew Baker, MD, Kaiser Permanente Medical Center, 27400 Hesperian Blvd, Hayward, CA 94545; (415) 784-4521.

SAN DIEGO, CALIFORNIA. BE/BC OB/GYN position available with an all-women OB/GYN group. Guaranteed 1st year salary with paid malpractice. Outstanding opportunity to join a fee-for-service private practice group. Send CV to Dr M. Benoni, 3023 Bunker Hill, Ste 203, San Diego, CA 92109; or call (619) 581-2225.

(Continued on Page 377)

(Continued from Page 376)

PART-TIME MEDICAL CONSULTANT CONTRACTS

Physicians needed to work under contract, on a part-time basis for the Social Security Administration's Disability Insurance Program. Involves review of medical evidence in disability claims at 100 Van Ness Avenue, San Francisco, California. No patient contact. Applicants must: (1) have a valid license to practice medicine in the USA; (2) have recent or current clinical experience; and (3) be available between 7:00 am and 4:30 pm, Monday through Friday for case review. Subject to change, the specialties needed are Psychiatry, Otolaryngology, and Rheumatology. Women and minorities are encouraged to apply. If interested in receiving further information, submit written request by September 21, 1988 to

Contract Officer
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INDUSTRIAL PHYSICIAN

Would you like to live in the Rocky Mountains in an area that is unsurpassed in outdoor recreational opportunities? EG&G Idaho is the prime operating contractor for the U.S. Department of Energy at the Idaho National Engineering Laboratory. We are located in the vicinity of Sun Valley, Jackson Hole and the Yellowstone & Teton National Parks.

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QUALIFICATIONS: Board Certification or Board Eligibility in Occupational Medicine, Family Practice, Internal Medicine, or Emergency Medicine is desirable. Must have current license and be eligible to become licensed in the state of Idaho.

COMPENSATION: Forty hour week with generous benefits and compensation package.

If interested and qualified, please send C.V. and salary requirements to: **Employment Services (WLS-26), EG&G Idaho, Inc., P.O. Box 1625, Idaho Falls, Idaho 83415.** We are an equal opportunity employer M/F/H/V. U.S. citizenship required.

EG&G Idaho Inc.

NEUROLOGIST. Medical-legal evaluations for traumatic injury patients. California license required. Lucrative fee for service with high growth potential. Contact Director, PO Box 14046, San Francisco, CA 94114.

INTERNIST/FAMILY PRACTITIONER sought by Fircrest School for the Developmentally Disabled. Chronic care. Interdisciplinary team setting. Submit résumé to R. Doan, MD, Fircrest School, 15230 15th N.E., Seattle, WA 98155. Apply Fircrest Personnel, (206) 364-0300, ext 430. EOE.

FAMILY PRACTITIONER, JUNEAU, ALASKA. Busy four physician Family Practice group (including OB) seeks replacement for partner departing fall 1988. Located in Alaska's capital city in the Tongass National Forest, offering year 'round recreation including skiing, boating, and hiking. Guaranteed salary with excellent fringe benefits and opportunity for partnership within one year. Send CV to Sarah A. Isto, MD, Valley Medical Care, Inc, 9309 Glacier Hwy, B-301, Juneau, AK 99801; (907) 789-3181.

ORTHOPEDIC SURGEON NEEDED

Excellent private practice opportunity for BC/BE Orthopedist. Financial incentives, guaranteed income. 90,000 service area population with proven earning potential. Located in central California's San Joaquin Valley, Tulare offers family environment, superior lifestyle, attractive real estate prices, and abundant recreation in a steadily growing community. Please send CV or call:

Tulare District Hospital Physician Recruiting Office, PO Box 90112, Los Angeles, CA 90009; (213) 216-2687.

RURAL EASTERN WASHINGTON. Two physicians (BE/BC Family Practitioners) to take over successful Family Practice clinic, located just one-half mile from a modern 22-bed community hospital. Supportive, friendly farming community 58 miles west of Spokane. Offering unlimited year 'round recreation, excellent schools, affordable housing. Benefits include first year salary leading to early shareholder status, paid CME, five weeks vacation. Contact Colleen Mooney, Rockwood Clinic, TAF C-13, Spokane, WA 99220-4013; (509) 448-1304.

PHYSICIANS WANTED IN SACRAMENTO, CALIFORNIA. BC Orthopedic Surgeon, Neurosurgeon, and California licensed Psychologist with PhD for busy disability evaluation office in Sacramento, California. Excellent benefits, flexible work schedule, part- or full-time, great family and medical environment. Send CV to Medical Director, PO Box 160408, Sacramento, CA 95816.

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WOMEN'S HEALTH CENTER in Pleasanton, California seeking a Primary Care Physician. Full-time or part-time. Good salary. Lovely community 40 minutes from San Francisco. Contact Bonnie Rathjen, MD, (415) 463-3442.

PEDIATRICIAN. Locum tenens full- or part-time employment with a good future! Association and partnership. Solo practice, Burbank. 2625 W. Alameda Ave, Ste 420, CA 91505; (818) 843-6203, Dr Resnik.

CARDIOLOGIST NORTHERN ARIZONA

A busy, well-established invasive Cardiologist in Cottonwood, Arizona is seeking an invasive or non-invasive Cardiologist to join him. He is the only Cardiologist in a service area of 15,000 and refers his caths and surgical patients to the Arizona Heart Institute in Phoenix. Cottonwood is located 35 miles south of Flagstaff, 18 miles west of Sedona, and 85 miles north of Phoenix.

For further information about this private practice opportunity, send your CV to: Manager, Professional Relations, Humana Inc., Dept. HH-9, 500 West Main Street, Louisville, KY 40201-1438. Or call TOLL-FREE 1-800-626-1590.

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EMERGENCY MEDICINE—MONTANA. Stable, established four physician group expanding, seeks fifth career-oriented Emergency Physician for modern 120-bed full-service hospital. 15,000 visits per year. Quality oriented, progressive practice in university community of western Montana. Flexible scheduling. Competitive compensation package including malpractice insurance. Opportunity for program development. Unlimited recreational opportunities. For information or to send CV: Frank L. Walker, MD, Missoula Community Medical Center, 2827 Fort Missoula Rd, Missoula, MT 59801; (406) 728-4100.

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The Wenatchee Valley Clinic, a multispecialty group of 105 physicians, has several practice opportunities throughout its seven practice locations. Currently we are seeking:

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All positions offer an excellent compensation and benefit package. North central Washington provides a high quality of life for those interested in an abundance of recreational opportunities in a family-oriented rural setting. If interested, send your CV to Dr Gerald Gibbons, Medical Director, Wenatchee Valley Clinic, 820 N. Chelan Ave, Wenatchee, WA 98801, or call (509) 663-8711, ext 205.

(Continued on Page 382)

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Well-controlled clinical trials confirm:

ZANTAC 150 mg hs significantly superior to cimetidine 400 mg hs for maintenance therapy in healed duodenal ulcers.

FREE FUTURE

Percent of patients ulcer-free after 1 year of therapy

ZANTAC 150 mg hs (n = 60)	84%*
cimetidine 400 mg hs (n = 66)	57%
ZANTAC 150 mg hs (n = 243)	77%†
cimetidine 400 mg hs (n = 241)	63%

*P = 0.01 †P = 0.0004 % life-table estimates

All patients were permitted prn antacids for relief of pain.
Adapted from Silvis[1] and Gough.[2]

These two trials[1,2] used the currently recommended dosing regimen of cimetidine (400 mg hs) and ranitidine (150 mg hs). A comparison of other dosing regimens has not been studied.
The studied dosing regimens are not equivalent with respect to the degree and duration of acid suppression or suppression of nocturnal acid.
The superiority of ranitidine over cimetidine in these trials indicates that the dosing regimen currently recommended for cimetidine is less likely to be as successful in maintenance therapy.

Zantac® 150

ranitidine HCl/Glaxo 150 mg tablets hs

Glaxo/ ROCHE

See next page for references and Brief Summary of Product Information.

References: 1. Silvis SE, Griffin J, Hardin R, et al. Final report on the United States multicenter trial comparing ranitidine to cimetidine as maintenance therapy following healing of duodenal ulcer. *J Clin Gastroenterol* 1985;7(6):482-487. 2. Gough KR, Korman MG, Bardhan KD, et al. Ranitidine and cimetidine in prevention of duodenal ulcer relapse: A double-blind, randomised, multicentre, comparative trial. *Lancet* 1984;2:659-662.

ZANTAC® 150 Tablets
(ranitidine hydrochloride)

ZANTAC® 300 Tablets
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in ZANTAC® product labeling.

INDICATIONS AND USAGE: ZANTAC® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within four weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (eg, Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within six weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD).** Symptomatic relief commonly occurs within one or two weeks after starting therapy. Therapy for longer than six weeks has not been studied.

In active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, and GERD, concomitant antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy.
2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during ZANTAC therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH-dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2,000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next nine weeks.

Pregnancy: *Teratogenic Effects: Pregnancy Category B:* Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65 to 82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC®. The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported.

Cardiovascular: Rare reports of tachycardia, bradycardia, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, and abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg qid IV for seven days, and in 4 of 24 subjects receiving 50 mg qid IV for five days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Reversible blood count changes (leukopenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. Rare cases of agranulocytosis or of pancytopenia, sometimes with marrow hypoplasia, have been reported.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia) and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg twice daily. An alternate dosage of 300 mg once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.

Maintenance Therapy: The current recommended adult oral dosage is 150 mg at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer ZANTAC® 150-mg doses more frequently. Doses should be adjusted to individual patient needs, and should continue as long as clinically indicated. Doses up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice a day.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: ZANTAC® 300 Tablets (ranitidine hydrochloride equivalent to 300 mg of ranitidine) are yellow, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0393-40) and unit dose packs of 100 tablets (NDC 0173-0393-47).

ZANTAC® 150 Tablets (ranitidine hydrochloride equivalent to 150 mg of ranitidine) are white tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

May 1988

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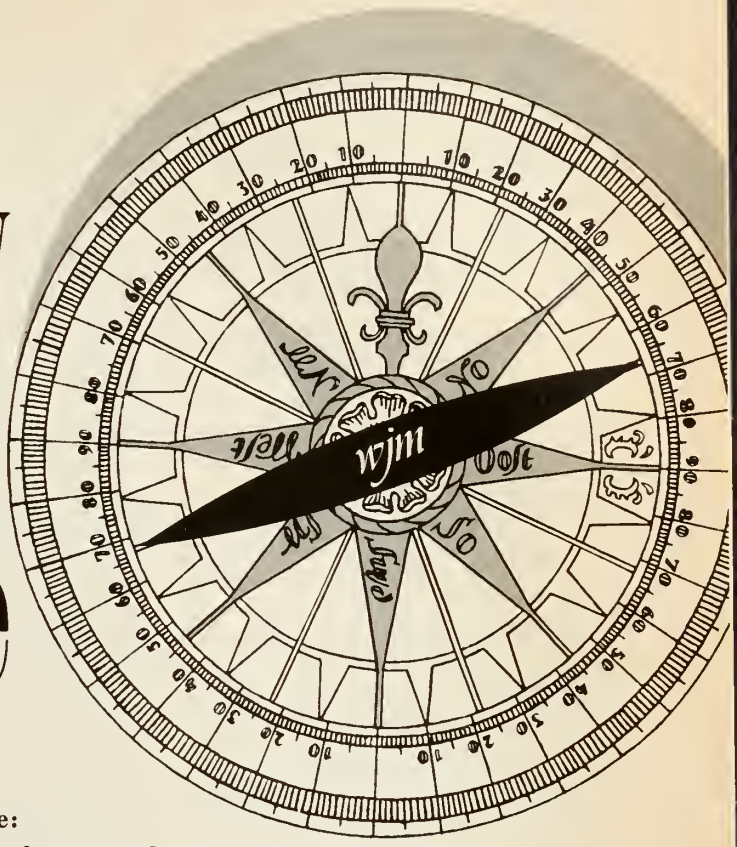

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(Continued from Page 377)

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EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine is recruiting for a full-time faculty. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine is undergoing rapid academic development, and is applying to have an approved residency training program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is an EMT-II Base Station and Training Center, and in addition, provides medical direction for the Hospital's Helicopter Program. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. Candidates should have proven teaching ability and clinical research interest. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair of Emergency Medicine Search Committee, Tr. 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. This position will be open until filled; however, applications will not be accepted after June 30, 1989. The University of California is an Affirmative Action/Equal Opportunity Employer.

CHAIRMAN, DEPARTMENT OF INTERNAL MEDICINE, KERN MEDICAL CENTER. A county teaching hospital is seeking a chairman for this UCLA affiliated department. Nine full-time faculty, 18 residents in fully accredited program. Qualifications: Board Certification in Internal Medicine, established record of scholarly achievement in teaching and patient care, and demonstrated management skills. Must be eligible for appointment to senior faculty position at UCLA and for licensure in California. Address inquiries with CV to Joseph Ansfield, MD, Chairman, Search Committee, Medical Staff Office, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

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Primary Care Physicians needed to work as *locum tenens* in northern California. Radiologists needed statewide. High salary, paid malpractice. Work whenever you like. Permanent placements as well.

Contact Carol Sweig, Director, (415) 673-7676. Western Physicians Registry, 710 Van Ness Ave, San Francisco, CA 94102.

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FAMILY PRACTICE, CASHMERE, WASHINGTON. Family Practitioner for two MD office. Vacancy opening July 1989. Cashmere is on the eastern edge of the Cascades 10 miles west of Wenatchee, our 167-bed hospital location. It's a scenic spot in a fruit-growing valley. Schools are highly rated and recreation is tops. Call duty will be shared with two MDs in a separate office. Please contact Edgar A. Meyer, MD, 303 Cottage Ave, Cashmere, WA 98815; (509) 782-1541 or 782-2571.

12 PHYSICIAN MULTISPECIALTY GROUP located in beautiful Marin County with two OB/GYNs is seeking a third OB/GYN for association leading to partnership. Group practice is primarily fee-for-service. Call Bill Adamson, (415) 454-9100, or send CV to the San Rafael Medical Group, 1540 Fifth Ave, San Rafael, CA 94901-1847.

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Immediate and mid-1989 positions available for BC/BE General Internists. Due to rapid program expansion, we are seeking candidates for 3- to 12-month locum tenens and regular, full-time staff positions.
Northwest Permanente, P.C., is affiliated with the Kaiser Permanente program in Oregon and Washington. Kaiser Permanente is the oldest and largest HMO of its kind in the country, with programs in 15 states and the District of Columbia. In this region we have over 320,000 enrolled members, two hospitals and 11 outpatient facilities located primarily in the Portland area. Northwest Permanente is a professional corporation of 385 physicians who contract exclusively to provide care for the members of Kaiser Permanente. We provide a stimulating professional environment, a quality lifestyle in the Pacific Northwest, and an attractive salary and benefit package.
If you would like to pursue one of the above positions, please forward your CV and letter of inquiry for an immediate response to:

Fred M. Nomura, MD
Regional Medical Director
Northwest Permanente, P.C.
3600 N. Interstate Ave
Portland, OR 97227

PHYSICIANS WANTED

FAMILY PRACTICE PHYSICIAN (BC/BE) to join four-site four physician practice at community/migrant health center in large agricultural valley surrounded by mountains in southern New Mexico bordering Texas and Mexico. City (65,000 population) has state university and military contract industry; good job opportunities for spouse. Full Family Practice with limited OB and in-patient care at local 268-bed hospital. Center serves as teaching site for various health and medical students. Center is a loan repayment program which may defray $20,000 per year. Competitive salary with good benefits which include pension, malpractice, health insurance, CME, and others. Send CV to Mary E. Bane, Project Director, La Clinica de Familia, PO Drawer D, San Miguel, NM 88058; (505) 233-4270. Start date July/August 1989.

(Continued on Page 384)

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ADVANCES IN FERTILITY AND STERILITY—Proceedings of the 12th World Congress on Fertility and Sterility, Singapore, October 1986. 6 volumes (vol 1—Ovulation and Early Pregnancy; vol 2—In Vitro Fertilisation and Other Alternative Methods of Conception; vol 3—Releasing Hormones and Genetics and Immunology in Human Reproduction; vol 4—Infertility—Male and Female; vol 5—Endometriosis and Other Disorders and Infections; vol 6—Contraception). Series edited by S. S. Ratnam and E. S. Teoh, National University Hospital, Singapore. Parthenon Publishing, 120 Mill Rd, Park Ridge, NJ 07656, 1987. $55 per volume; $275 for set of 6 volumes.

AIDS: A GUIDE FOR THE PRIMARY PHYSICIAN—Edited by King K. Holmes, MD, PhD, Chief, Department of Medicine, Harborview Medical Center, and Professor and Vice-Chairman, Department of Medicine, University of Washington, and Arno G. Motulsky, MD, ScD, Professor of Medicine and Genetics and Director, University of Washington Center for Inherited Diseases, Seattle. University of Washington Press, PO Box 50096, Seattle, WA 98145-5096, 1988. 65 pages, $15 (paperback).

BREAST CANCER—COLLABORATIVE MANAGEMENT—Edited by Jay K. Harness, MD, Clinical Associate Professor, Department of Surgery, and Director, Breast Care Center; Harold A. Oberman, MD, Professor and Head, Section of Clinical Pathology, Department of Pathology; Allen S. Lichter, MD, Professor and Chairman, Department of Radiation Oncology; Dorit D. Adler, MD, Assistant Professor and Director, Division of Mammography, Department of Radiology; and Robert L. Cody, MD, Instructor, Division of Hematology/Oncology, University of Michigan Medical School, Ann Arbor. Lewis Publishers, Inc, 121 S Main St, PO Drawer 519, Chelsea, MI 48118, 1988. 380 pages, $69.95.

CARING FOR THE DISABLED ELDERLY—WHO WILL PAY?—Alice M. Rivlin and Joshua M. Wiener. The Brookings Institution, 1775 Massachusetts Ave, NW, Washington, DC 20036-2188, 1988. 309 pages; $29.95 (cloth), $11.95 (paper).

COLOR ATLAS OF CO2 LASER SURGICAL TECHNIQUES—Edited by Raymond J. Lanzafame, MD, Assistant Professor of Surgery, University of Rochester, and Program Director, CO2 Laser Training, Rochester General Hospital, and J. Raymond Hinshaw, MD, DPhil (Oxon), Professor of Surgery, University of Rochester, and Chief of Surgery, Rochester General Hospital, Rochester, New York. Ishiyaku EuroAmerica, Inc, 716 Hanley Industrial Court, St Louis, MO 63144, 1988. 297 pages, $145.

COMMON SKIN DISORDERS—A PHYSICIAN'S ILLUSTRATED MANUAL WITH PATIENT INSTRUCTION SHEETS—Third Edition—Ernst Epstein, MD, Clinical Associate Professor of Dermatology, University of California, San Francisco, School of Medicine. Medical Economics Books, Oradell, NJ 07649, 1988. 110 pages, $35.95 (paperback).

THE "DISCOVERY" OF SUDDEN INFANT DEATH SYNDROME—LESSONS IN THE PRACTICE OF POLITICAL MEDICINE—Abraham B. Bergman, MD, Professor of Pediatrics, University of Washington, Seattle. University of Washington Press, PO Box 50096, Seattle, WA 98145-5096, 1988. 231 pages, $12.50 (paperback).

DISEASES OF THE COLON, RECTUM, AND ANAL CANAL—Edited by Joseph B. Kirsner, MD, PhD, MACP, Louis Block Distinguished Service Professor of Medicine, University of Chicago, and Roy G. Shorter, MD, FRCP, FACP, FRCPath, Professor of Medicine and Pathology, Mayo Medical School, Rochester, Minnesota. Williams & Wilkins, PO Box 23291, Baltimore, MD 21203, 1988. 703 pages, $115.

DRUG INTERACTIONS INDEX—Second Edition—Robert T. Weibert, PharmD, Associate Clinical Professor, University of California, San Francisco, School of Pharmacy, San Diego Program, and William A. Norcross, Associate Clinical Professor of Community and Family Medicine, University of California, San Diego, School of Medicine. Medical Economics Books, Oradell, NJ 07649, 1988. 375 pages, $27.95 (paperback).

ELECTROMYOGRAPHY—NEUROMUSCULAR TRANSMISSION STUDIES—Shin J. Oh, MD, Professor of Neurology and Director, EMG and Evoked Potentials Laboratory and Muscle Histopathology Laboratory, University of Alabama and Veterans Administration Medical Center, Birmingham. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1988. 291 pages, $49.95.

ENDOCRINOLOGY AND MALIGNANCY—BASIC AND CLINICAL ISSUES—Proceedings of the First International Congress on Cancer and Hormones, Rome, April 1986—Edited by E. E. Baulieu, S. Lacobelli, and W. L. McGuire. Parthenon Publishing, 120 Mill Rd, Park Ridge, NJ 07656, 1986. 569 pages, $75.

FETAL ECHOCARDIOGRAPHY—AN ATLAS—Kathryn L. Reed, MD; Caroline F. Anderson, RDMS; and Lewis Shenker, MD, Department of Obstetrics and Gynecology, University of Arizona, Tucson. Alan R. Liss, Inc, 41 E 11th St, New York, NY 10003, 1988. 133 pages, $62.50.

GRAND ROUNDS—ONE HUNDRED YEARS OF INTERNAL MEDICINE—Edited by Russell C. Maulitz, Staff Physician, Presbyterian-University of Pennsylvania Medical Center, and Lecturer in History and Sociology of Science in Medicine, University of Pennsylvania School of Medicine, and Diana E. Long, Director of the Francis C. Wood Institute of the College of Physicians and Adjunct Associate Professor, University of Pennsylvania, Philadelphia. University of Pennsylvania Press, Bockley Hall, 13th Floor, 418 Service Dr, Philadelphia, PA 19104, 1988. 367 pages, $34.95.

GYNECOLOGIC SURGERY—Edited by Luis E. Sanz, MD, Associate Professor, Department of Obstetrics and Gynecology, Georgetown University School of Medicine, Washington, DC. Medical Economics Books, Oradell, NJ 07649, 1988. 439 pages, $57.

GYNECOLOGICAL ENDOCRINOLOGY—Proceedings of the First International Congress on Gynecological Endocrinology, Madonna di Campiglio, Italy, March 1986—Edited by A. R. Genazzani, A. Volpe, and F. Facchinetti, Department of Obstetrics and Gynecology, University of Modena, Italy. Parthenon Publishing, 120 Mill Rd, Park Ridge, NJ 07656, 1987. 694 pages, $95.

KLINEFELTER'S SYNDROME IN CHILDHOOD, ADOLESCENCE AND YOUTH—A GENETIC, CLINICAL, DEVELOPMENTAL, PSYCHIATRIC AND PSYCHOLOGICAL STUDY—Kurt Sørensen, Cytogenetic Laboratory, Psychiatric Hospital in Arhus, Risskov, Denmark. Parthenon Publishing, 120 Mill Rd, Park Ridge, NJ 07656, 1988. 291 pages, $75.

MANAGEMENT OF COMMON PROBLEMS IN OBSTETRICS & GYNECOLOGY—Second Edition—Edited by Daniel R. Mishell, Jr, MD, Professor and Chairman, and Paul F. Brenner, MD, Professor, Department of Obstetrics and Gynecology, University of Southern California School of Medicine, Los Angeles. Medical Economics Books, Oradell, NJ 07649, 1988. 673 pages, $42.95 (soft cover).

MEDICAL ECONOMICS ENCYCLOPEDIA OF PRACTICE AND FINANCIAL MANAGEMENT—Second Edition—Edited by Lawrence Farber. Medical Economics Books, Oradell, NJ 07649, 1988. 1, 241 pages, $79.

MEDICINE—DIAGNOSIS AND TREATMENT—Edited by Robert W. Schrier, MD, Professor and Chairman, Department of Medicine, University of Colorado School of Medicine, Denver. Little, Brown and Company, 34 Beacon St, Boston, MA 02108, 1988. 536 pages, $25 (paperback).

ORAL CONTRACEPTION IN PERSPECTIVE—THIRTY YEARS OF CLINICAL EXPERIENCE WITH THE PILL—A. D. G. Gunn, Director of Student Health, University of Reading, England. Parthenon Publishing, 120 Mill Rd, Park Ridge, NJ 07656, 1987. 149 pages, $38.

A PRACTICAL HANDBOOK FOR THE TREATMENT OF DEPRESSION—Edited by Desmond Kelly, MD, FRCP, FRCPsych, The Priory Hospital, London, and Richard France, MBBS, DObst, RCOG, Yateley Medical Centre, Near Camberley, Surrey, England. Parthenon Publishing, 120 Mill Rd, Park Ridge, NJ 07656, 1987. 205 pages, $45.

REGULATORY ROLES OF OPIOID PEPTIDES—Edited by P. Illes and C. Farsang. VCH Publishers, Inc, 220 E 23rd St, Suite 909, New York, NY 10010, 1988. 540 pages, $98.

RESEARCH ON GYNECOLOGICAL ENDOCRINOLOGY—Selected Free Communications Presented at the 1st International Congress of Gynecological Endocrinology, Madonna di Campiglio, Italy, March 1986—Edited by A. R. Genazzani, A. Volpe, and F. Facchinetti, Department of Obstetrics and Gynecology, University of Modena, Italy. Parthenon Publishing, 120 Mill Rd, Park Ridge, NJ 07656, 1987. 687 pages, $68.

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(Continued from Page 382)

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 3-8, 1989, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 15-17, 1988, Marriott City Center, Denver.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 10-12, 1988, Kauai Surf, Kauai.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: 1989, date and place to be announced.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 29-October 1, 1988, Heritage Inn, Great Falls.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1989, date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 11-14, 1989, Holiday Inn Pyramid, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): November 6-8, 1988, Portland.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 21-24, 1988, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 15-18, 1988, Yakima.

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Rocephin® ROCHE® IV·IM

ceftriaxone sodium/Roche

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep pneumoniae, Streptococcus* species (excluding enterococci), *Staph aureus, H influenzae, H parainfluenzae, Klebsiella* species (including *K pneumoniae*), *E coli, E aerogenes, Proteus mirabilis* and *Serratia marcescens*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph aureus, Staph epidermidis, Streptococcus* species (excluding enterococci), *E cloacae, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E coli, Proteus mirabilis, Proteus vulgaris, M morganii* and *Klebsiella* species (including *K pneumoniae*).

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains

PELVIC INFLAMMATORY DISEASE caused by *N gonorrhoeae*

BACTERIAL SEPTICEMIA caused by *Staph aureus, Strep pneumoniae, E coli, H influenzae* and *K pneumoniae*

BONE AND JOINT INFECTIONS caused by *Staph aureus, Strep pneumoniae, Streptococcus* species (excluding enterococci), *E coli, P mirabilis, K pneumoniae* and *Enterobacter* species

INTRA-ABDOMINAL INFECTIONS caused by *E coli* and *K pneumoniae*

MENINGITIS caused by *H influenzae, N meningitidis* and *Strep pneumoniae* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph epidermidis* and *E coli*

SURGICAL PROPHYLAXIS Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (e g , vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (e g , during coronary artery bypass surgery)

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure

SUSCEPTIBILITY TESTING Before instituting treatment with Rocephin appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug Therapy may be instituted prior to obtaining results of susceptibility testing

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad-spectrum antibiotics), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis Cholestyramine and colestipol resins have been shown to bind to the toxin *in vitro*

Mild cases of colitis respond to drug discontinuance alone Moderate to severe cases should be managed with fluid electrolyte and protein supplementation as indicated

When the colitis is not relieved by drug discontinuance or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should also be considered

Rarely, shadows suggesting sludge have been detected by sonograms of the gallbladder in asymptomatic and symptomatic patients This appears to be reversible on discontinuation of therapy In a few symptomatic patients receiving higher than usual doses, who underwent surgery, sludge containing traces of ceftriaxone was recovered from surgical specimens Discontinue therapy in patients who develop signs or symptoms suggestive of gallbladder disease, consider conservative management

PRECAUTIONS: *GENERAL* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology) Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically If evidence of accumulation exists, dosage should be decreased accordingly

Dosage adjustments should not be necessary in patients with hepatic dysfunction, however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin Patients with impaired vitamin K synthesis or low vitamin K stores (e g , chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed The maximum

ROCEPHIN* (ceftriaxone sodium/Roche)

duration of animal toxicity studies was six months

Mutagenesis Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone Ceftriaxone showed no potential for mutagenic activity in these studies

Impairment of Fertility Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day

PREGNANCY Teratogenic Effects Pregnancy Category B Reproductive studies have been performed in mice and rats at doses up to 20 times the usual human dose and have no evidence of embryotoxicity, fetotoxicity or teratogenicity In primates, no embryotoxicity or teratogenicity was demonstrated at a dose approximately three times the human dose There are, however, no adequate and well-controlled studies in pregnant women Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nonteratogenic Effects In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less

NURSING MOTHERS Low concentrations of ceftriaxone are excreted in human milk Caution should be exercised when Rocephin is administered to a nursing woman

PEDIATRIC USE Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section *In vitro* studies have shown ceftriaxone like some other cephalosporins, can displace bilirubin from serum albumin Exercise caution before administration to hyperbilirubinemic neonates, especially prematures

ADVERSE REACTIONS: Rocephin is generally well tolerated In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%) Less frequently reported (less than 1%) was phlebitis after I V administration

HYPERSENSITIVITY—rash (1 7%) Less frequently reported (less than 1%) were pruritus, fever or chills

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5 1%) and leukopenia (2 1%) Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time

GASTROINTESTINAL—diarrhea (2 7%) Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia

HEPATIC—elevations of SGOT (3 1%) or SGPT (3 3%) Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin

RENAL—elevations of the BUN (1 2%) Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%)

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%)

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%)

Other rarely observed adverse reactions (less than 0 1%) include leukocytosis, lymphocytosis, monocytosis, basophilia a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria anaphylaxis, bronchospasm serum sickness, abdominal pain colitis, flatulence, dyspepsia palpitations and epistaxis

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection The total daily dose should not exceed 4 grams

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared The usual duration is 4 to 14 days, in complicated infections longer therapy may be required

In the treatment of meningitis a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days

No dosage adjustment is necessary for patients with impairment of renal or hepatic function, however, blood levels should be monitored in patients with severe renal impairment (e g dialysis patients) and in patients with both renal and hepatic dysfunctions

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles The following packages are available

Vials containing 250 mg 500 mg 1 gm or 2 gm equivalent of ceftriaxone, piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone, bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION)

Also supplied as a sterile crystalline powder as follows

ADD-Vantage Vials** containing 1 gm or 2 gm equivalent of ceftriaxone

Also supplied premixed as a frozen iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose plastic containers,† as follows

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1 9 gm dextrose hydrous, USP added

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1 2 gm dextrose hydrous, USP added

NOTE Rocephin in the frozen state should not be stored above -20°C

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†Manufactured for Roche Laboratories, Division of Hoffmann-La Roche Inc , by Travenol Laboratories, Inc , Deerfield, Illinois 60015

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